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ABSTRACT

This publication summarizes the activities of the most recent meeting of the nation's most influential drug abuse professionals and measures progress in a variety of areas. Outcomes of symposia, meetings, and presentations are discussed. Symposia include: (1) "Is Dopamine the Answer? Evidence for the Importance of Other Systems in the Reinforcing/Neurochemical Effects of Psychostimulants" (S. Izenwasser and Y. Itzhak); (2) "Substance Abuse, Immunomodulation and Infections"(H. Friedman and T. K. Eisenstein); (3) "hat Are They Thinking? The Mediating Role of Parental Cognitions in the Parenting Processes of Drug-Dependent Mothers and Fathers"(N. E. Suchman and T. J. McMahon); (4) "rug Reward in Humans: What Does Dopamine Do?"(H. deWit); (5) "Medical Consequences of Problems of Drug Dependence" (D. J. Jones and S. Genser); (6) "Understanding the Abuse-Relevant Effects of Drugs: Studies by Young Investigators" (P. W. Czoty and K. M. Wilcox); (8) "Prescription Drug Abuse: What Do We Know?" (S. Schnoll and F. Sapienza); (9) "Cocaine Addiction: To the Amygdala and Beyond" (K. M. Kantak and F. Weiss); (10) "Longitudinal Studies of Pathways to Drug Abuse: Current Status, Emerging Findings, and Implications for Prevention" (J. D. Colliver and M. D. Glantz); (11) "Drugs and Crime" (R. A. Millstein and L. Erinoff); (12) "Violence Exposure and Substance Abuse" (W. Klieweer and D. Svikis); (13) "Neuropeptidergic Responses to Psychostimulant Drugs of Abuse: Strategies for Drug Development" (R. S. Rapaka and G. R. Hanson); (14) "The New Thing: Applying Information Technologies to Drug Abuse Prevention and Treatment" (W. K. Bickel and A. T. McLellan); (15) "French Experience with Buprenorphine" (E. C. Strain and H. W. Clarke); and (16) "Drug Choice: What We Know and What We Need to Know" (S. S. Negus and W. L. Woolverton). (GCP)

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Problems of Drug Dependence, 2002:
Proceedings of the 64th Annual Scientific Meeting, The College on Problems of Drug Dependence, Inc.

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Dr. William L. Dewey, Department of Pharmacology and Toxicology, Virginia Commonwealth University was the editor of this monograph.

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INTRODUCTION OF THE NATHAN B. EDDY MEMORIAL AWARD RECIPIENT

E. L. Way

A defining moment for any proud teacher is to bask in the reflected glory of a former pupil. It is my pleasure to introduce Horace H. Loh, the 2002 Nathan B. Eddy Memorial Award recipient. Over the past 30 years, his creative activity has had a major impact on our understanding of how opioid drugs act at the cellular and molecular level. His research has provided fundamental knowledge about the neurochemical mechanisms of opiate action, the molecular nature of the opioid receptors, their gene structures, and the pharmacology and functions of endogenous opioid peptides. He has published over 450 original research papers in leading scientific journals with many collaborators. The impact of his work is attested to by the fact that he was included among the most-cited life and physical scientists for the past ten years by the Institute for Scientific Information's Science Citation Index. It is not surprising, therefore, that he is in great demand worldwide as a speaker at symposia, workshops and seminars. His scientific accomplishments have been recognized by professional organizations almost as prestigious as CPDD, among which include the American Society for Pharmacology and Experimental Therapeutics (ASPET), the Pharmaceutical Research and Manufacturers of America (PhRMA), the Humboldt Award from Germany and, repeatedly over the years, by the Pope and Godfather of substance abuse – NIDA.

After consorting with agricultural chemists at Iowa and acquiring a Ph.D. in Biochemistry in 1965, Loh found a "*way*" at UCSF to shift from farming to pharmacology and became hooked on opiates. His early efforts with his connections there culminated in the development of simple methodologic innovations that found wide application and promoted fundamental studies on the biologic mechanisms involved in opiate tolerance and physical dependence. The development of a pellet implantation procedure enabled the rapid induction of a high degree of tolerance to and physical dependence on morphine for easy quantification in a large number of experimental animals. Likewise, with C. H. Li and E. T. Wei, the innovative use of osmotic minipumps to deliver minute doses of drugs directly into various brain regions facilitated the delineation of the pharmacologic profile of β-endorphin and established that it possesses morphine-like properties, including dependence liability. Additionally, in association with N. Lee and others, the functional role of dynorphin was characterized and found to have a unique modulatory role in regulating pain, respiratory function and immunologic activity. Loh has since carried his interests well beyond these early investigations and in recent years has contributed an extraordinary amount of knowledge that is on the cutting edge of science which I shall discuss in brief with respect to the characterization of opiate receptor signaling, opioid receptor genes and molecular mechanisms involved in acute and chronic opioid action.

Characterization of opiate receptor signaling

In collaboration with Ping-Yee Law, multiple opioid receptor binding sites were found to exist and the G-protein dependent coupling of the opiate receptor to adenylyl cyclase in brain was demonstrated conclusively. From mutational analyses of the receptors, the transmembrane domains involved in regulating opioid ligand's intrinsic efficacies were identified. One of the most striking mutations was the conserved serine mutation in the 4th transmembrane domain to leucine or alanine resulted in the ability of classical antagonists, such as naloxone or naltrexone, to exhibit agonistic properties. This property could be demonstrated in mice with "knock-in" serine mutant receptor. Currently the process of developing a gene therapy vehicle for the delivery of such antagonist-activated mutant receptors at the target sites *in vivo* is under study. This work has tremendous implications and should not only facilitate the elucidation of the molecular basis of opioid receptor activation, but may also lead to the selective design of analgesic drugs with less adverse effects.

Characterization of opiate receptor genes.

Loh and his colleagues have been the leaders in promoting an understanding of the regulation of opioid receptor gene expression. They were the first to clone and characterize the structures of all three opioid receptors' genes and by exploiting the knowledge to produce knock-out MOR-1 gene mice, the analgesic action of morphine was demonstrated to be via the μ-opioid receptor. In more recent work, multiple promoters of these genes have been identified and defined as well as the various negative and positive elements that control the expression of these genes. Such studies will not only enhance comprehension concerning the regulation of opioid receptor gene

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expression, but perhaps even more importantly, the recognition of the spatial and temporal expression of these genes will be of general importance in basic neurobiologic processes.

Molecular basis for opiate tolerance and physical dependence.

Loh published early and extensively implicating second messengers and different neurotransmitters in tolerance and physical dependent development. His recent findings, with Law, have largely defined and differentiated desensitization, internalization, and down-regulation receptor processes that are involved in opiate tolerance mechanisms. Also, the agonist-induced phosphorylation sites on the receptors involved in desensitization have been elucidated. Although phosphorylation of the G protein-coupled receptor kinases (GRKs) has been known to result in the desensitization of the receptor, Loh and Law have discovered that desensitization involves two processes, rapid and slow, with both receptor phosphorylation and internalization participating in the rapid desensitization. Thus, control of receptor phosphorylation after identification of the phosphorylation sites in tolerance development offers still another approach towards treatment.

In closing, it is necessary to point out that Loh's dedication to the field of substance abuse is not solely ivory towered. He is a triple threat quarterback with an impressive record as a teacher and scientific statesman. His fertile mind and inexhaustible energy attract and bring out the best in students, postdocs and peers and serve to make him an extremely influential and successful mentor; numerous students and trainees have gone on to successful careers of their own. Loh's distinguished record of service on both national and international levels exemplifies his commitment to addiction and treatment. He has served three terms as the chair of three different NIDA study sections and four years as a NIDA council member. He has also served the CPDD on the board of directors and scientific program committees. Internationally, he was the founding president of the Society of Chinese Bioscientists in America (SCBA), is called upon repeatedly to help organize the seminars and workshops for the International Narcotic Research Conference (INRC) and has been very active in formulating scientific policies for Taiwan, Hong Kong and China.

Science and academe aside, Horace has other possessions of distinction, namely, a crooner's voice that nearly gaffed me to substitute Nelson for Nathan for the Award today, a lovely historic home, previously owned by Willie Mays, who first crossed the racial barrier in a restricted San Francisco neighborhood, and, of course, Dana, the long-suffering bride of a junkie workaholic.

NATHAN B. EDDY MEMORIAL AWARD LECTURE

P.-Y. Law and H. H. Loh

University of Minnesota Medical School, Minneapolis, MN

STUDIES ON THE MOLECULAR MECHANISM OF OPIOID TOLERANCE: RECEPTOR DESENSITIZATION AND PHOSPHORYLATION

First of all, I feel deeply honored to receive the Nathan B. Eddy Memorial Award. I thank the CPDD and the award selection committee for the privilege of delivering this lecture. I also want to take this opportunity to thank my mentor, Professor Edward Leong Way, for getting me "hooked on morphine" for the past three decades. The enduring total support of my wife and children has been an absolute essential component of our work. I also want to thank my long-term collaborators, Professors Ping-Yee Law and Li-Na Wei, for the many contributions they have made in the work that I'm presenting today. Of course, we must not forget that any scientific effort requires the contributions of many individuals, and I am very grateful to the numerous outstanding and dedicated students, postdoctoral fellows, and the entire research staff with whom I have been so privileged to work.

During the past three decades, our laboratory has focused solely on the pharmacology of opioids, with specific emphasis on the Neurochemical mechanism of opioid tolerance. For the presentation today, I'll concentrate on a very limited aspect of our recent work on the regulation of opioid receptor activities that we believe is related to the mechanism of tolerance in vivo.

Opioid addiction is the consequence of a complex network of neuronal adaptational responses to the repeated exposure to the drug. It has important psychological and social causes and consequences. The process results in the development of complex behaviors such as drug tolerance, dependence, and craving for the opioid drugs that are characteristic of an addiction state. For many years, several laboratories, including our group, have focused their efforts to elucidate the molecular and cellular basis of addiction. Since drug dependence and craving are complex psychological and physiological phenomena, our emphases have been on the molecular mechanism for opioid tolerance.

There are many hypotheses on the molecular and cellular basis for opioid tolerance. A recent review by Nestler and Aghajanian (1) summarized the results in support of the various hypotheses. From the early hypothesis suggesting that the metabolic tolerance was the basis for opioid tolerance, to the recent one involving receptor internalization, the proposed hypotheses could be grouped into two major types: (1) the homeostasis theory, in which the drug disturbs the homeostasis and the drug effects are compensated by the activation of pathways that produced the opposite effects, thus restoring the homeostasis; and (2) a change in the drug receptor interaction, thus rendering the receptor less sensitive to the drug. In the homeostasis theory, macromolecules' syntheses, such as the transcriptional factor such as c-fos (2-5) or the neurotransmitters' activities such as the glutamatergic transmission (6-7) could be altered during chronic opiate treatment. The opiate drug receptor interaction could remain constant during the chronic agonist treatment. However, the homeostasis of the system can be restored also by the reduction of the receptor signals during chronic treatment. We favor this second hypothesis because all opiate actions are mediated by the receptor activation. Uncoupling of the receptor from the effector is an efficient mechanism for the blunting of the signals. Hence, our research focus has been on the mechanism and regulation of opioid receptor signaling.

Opioid receptor belongs to the subfamily of rhodopsin receptor within the super family of G protein-coupled receptors (GPCR). The signaling of the GPCR is tightly regulated, and normally involves the uncoupling of the receptor from the respective effector. A model in which a GPCR, such as β_2-adrenergic receptor activities, can be regulated has been proposed by Lefkowitz and his co-workers (8). In this model, agonist binding to the receptor results in the rapid phosphorylation of the receptor by protein kinases, including the G protein-coupled receptor kinases (GRK), thereby promoting the association of the cellular protein arrestin. Association of arrestin with the receptor not only uncoupled the receptor from the respective G protein that transduced the signal and thus blunted the receptor signaling (receptor desensitization), the arrestin molecule is also involved in the agonist-induced, clathrin-coated vesicles mediated receptor internalization. Within this endocytotic pathway, the agonist-induced receptor internalization is the initiation of receptor trafficking to other subcellular compartment such as lyzosomes where receptor degradation occurs. Subsequently, there is a decrease or down-regulation of the overall cellular receptor content. Arrestin also serves as an adapter molecule in the β_2-adrenergic receptor signaling such that a receptor-src kinase complex is formed through which activation of the MAP kinases Erk1 and Erk2 by the β_2-adrenergic receptor is accomplished (9). The activated MAP kinase can phosphorylate the β-arrestin and GRK. The phosphorylated forms of these proteins would not interact with the receptors, and thus serves as the feedback inhibition of the desensitization signals (10,11).

Opioid receptors appear to be regulated similarly as the β_2-adrenergic receptor. Chronic agonist treatment has resulted in the homologous desensitization of the δ-opioid receptor regulation of the adenylyl cyclase activity (12-14) GTPase activity (15), or μ-opioid receptor mediated increase in the K^+ conductance (16,17) in locus coeruleus neurons or the spike amplitude in the CA1 region of the rat hippocampus (18). The control of the Ca^{2+} current by μ-opioid receptor also exhibited homologous desensitization upon chronic treatment (19) The loss of these responses have been proposed to be due to the uncoupling of the receptor from the G protein as demonstrated by the decrease in the receptor in high affinity state (20,21) or by the decrease in the size of the receptor complex (22). Further, animals with the β-arrestin2 knockout appeared to have enhanced morphine response (23) and reduced tolerance development (24), thus suggesting the uncoupling of the receptor from its effector is related to the mechanism of morphine tolerance.

If the receptor uncoupling is the basis for the morphine tolerance development, then the cellular regulation of the opioid receptor activity must exhibit common characteristics as the regulation of other GPCRs. One general feature for the GPCR desensitization is the phosphorylation of the receptor upon agonist binding. Phosphorylation of the opioid receptors in the presence of agonists have been demonstrated (25-27). Though there is discrepancy in whether morphine could (28) or could not (27) induce phosphorylation of the μ-opioid receptor, the phosphorylation of the receptor correlates to the efficacy of the ligand (29). Thus, it is not too surprising that several laboratories reported that the phosphorylation of the receptor leads to rapid desensitization of the opioid responses (25,28). Activation of protein kinases such as Ca^{2+}/calmodulin-dependent kinase II (30) or MAP kinase (31) could lead to the desensitization of the receptor. Mutation of the Thr^{394}, a putative GRK site in μ-opioid receptor (32) or the last four Ser/Thr residues within the carboxyl domain of the δ-opioid receptor (33) resulted in the blunting of the agonist-induced desensitization of the receptor. Overexpression of the dominant negative mutant of GRK could also decrease the agonist-induced phosphorylation and attenuate the desensitization response (25). These studies and others support the hypothesis that receptor phosphorylation leads to the loss of response.

However, there are other reports that do not support phosphorylation of the receptor as the critical step in the loss of opioid responses. The time course of receptor phosphorylation that was rapid did not correlate with the desensitization of the receptor, which was slow (34). Overexpression of the GRK and arrestin did not increase this slow desensitization process (33,34). Deletion of the last 31 amino acids of δ-opioid receptor resulted in the abolition of both GRK- or PKC-mediated agonist-dependent phosphorylation of the receptor, but did not block the agonist-induced receptor desensitization (35,36). The complete mutation of all Ser/Thr residues within the 3rd intracellular loop and the C-terminus of μ-opioid receptor did not prevent DAMGO-induced receptor desensitization (37). Further, overexpression of β-arrestin 1 resulted in the blunting of the δ- and κ- but not μ-opioid receptor activity (38). The ability of μ-opioid receptor to associate with β-arrestin was demonstrated by studies reported by Whistler and von Zastrow (39) in which morphine could induce μ-opioid receptor endocytosis in the HEK293 cells overexpressed the β-arrestin. These data suggested that μ-opioid receptor might be desensitized via a pathway other than the receptor phosphorylation and arrestin binding pathway.

In order to resolve the controversies involved in the role of opioid receptor phosphorylation in the cellular regulation of opioid activities, we initiated the project to determine the specific amino acid residues being phosphorylated in the presence of agonists. We used site-directed mutagenesis approach to determine the sites of agonist-induced receptor phosphorylation of the μ-opioid receptor. Studies from other laboratories and ours have indicated that the probable phosphorylation sites lie within the carboxyl tail domain of the μ-opioid receptor. There are 12 Ser/Thr residues within the carboxyl tail. Hence, the first set of mutants we generated were those with cluster of Ser/Thr mutated to Ala residues. The mutants generated were: mutant I=Ser^{354} to Thr^{357} mutated to the Ala residues; mutant II= S363A and T364A mutations were added to mutant I; mutant III= T370A, S375A and T376A mutations were added to mutant II; and mutant IV= all the Ser/Thr residues within the carboxyl tail domain were mutated to Ala residues. These mutants were stably expressed in HEK293 cells. DAMGO-induced phosphorylation of these receptors was then determined. As summarized in *Figure 1*, removal of all Ser/Thr residues within the carboxyl tail resulted in the complete abolishment of agonist-induced receptor phosphorylation. Similarly, DAMGO could not induce phosphorylation of the receptor with all Ser/Thr residues converted to Ala with the exception of Thr^{379}, Thr^{383} and Thr^{394}. Conversion of the Thr^{394} to Ala did not alter the magnitude of DAMGO-induced receptor phosphorylation. These results clearly indicated that Thr^{394} could not be the site for agonist-induced phosphorylation. These results also suggest that phosphorylation of the μ-opioid receptor occurs at the Ser/Thr residues between Ser^{363} and Thr^{376}.

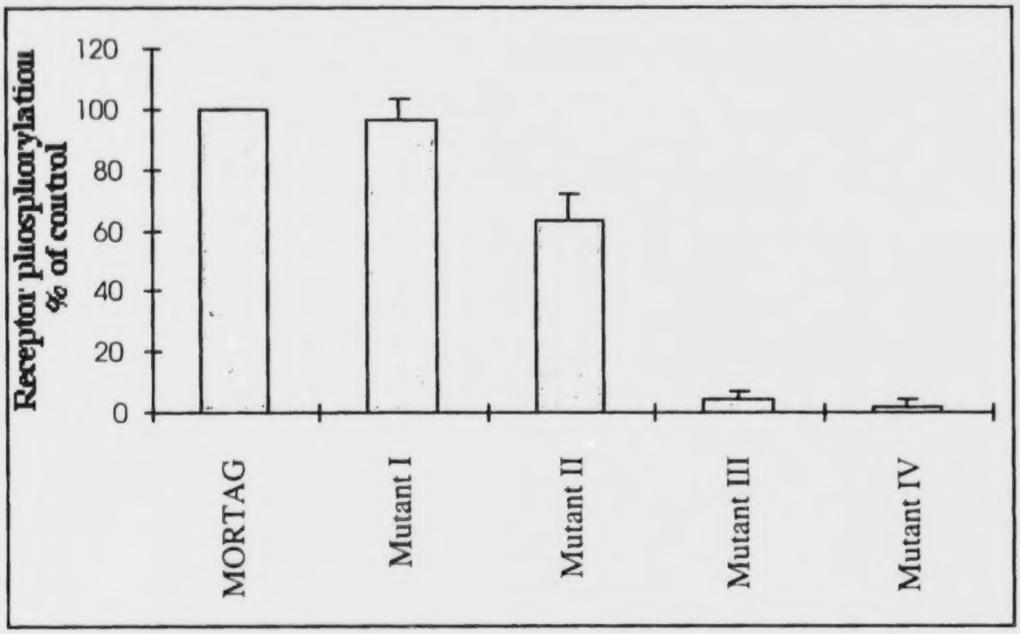


Figure 1. Agonist-induced phosphorylation of the wild-type and mutant opioid receptor. Hemagglutinin epitope-tagged μ-opioid receptors were stably expressed in HEK293 cells, metabolically labeled with $^{32}P_i$ and treated with 10 μM DAMGO for 15 minutes. Afterwards the cells were lysed and receptor extracted, and partially purified with wheat germ agglutinin column chromatography. The receptors were then immunoprecipitated, and separated from other cellular proteins by SDS-PAGE. Radioactivity associated with the receptor was determined by exposing phosphoimager's screen and normalized to the receptor protein content determined by western analyses. The values represented at 3 separate determinations.

Since the cluster mutants indicated that the agonist-induced phosphorylation sites are located between the Ser^{363} and Thr^{376} residues, we generated the single Ser or Thr mutants within this region so as to identify the phosphorylation sites. From these receptor mutant analyses, we have identified that Thr^{370} and Ser^{375} are the two amino acid residues that are phosphorylated in the presence of DAMGO. These two residues could be demonstrated to be the sites by the mutation of all Ser/Thr residues within the carboxyl tail domain of the μ-opioid receptor to Ala with the exception of these two residues. In those receptor mutants, DAMGO could induce the phosphorylation of the receptor. Whether these Ser/Thr residues are phosphorylated by the GRKs remain to be demonstrated. GRK has been demonstrated to phosphorylate Ser/Thr within the vicinity of acidic amino acid residues (40). The Ser^{375} does not have any acidic amino acid within the vicinity, while Thr^{370} is two residues upstream of the Glu^{372}, so it could be the substrate for the GRK. However, Ser^{375} immediately follows the Pro^{374} within the μ-opioid receptor sequence, and could not be a substrate for MAPK, which phosphorylates Ser/Thr residues immediate before a Pro. The striking feature for the agonist-induced phosphorylation of the μ-opioid receptor lies with the common feature it shares with the ∂-opioid receptor. Agonist DPDPE induced the phosphorylation of Thr^{358} and Ser^{363} residues within the carboxyl domain of the ∂-opioid receptor in a sequential manner. Though the sequences of the carboxyl tail domains between the μ- and ∂-opioid receptor are divergent, there appears to be a shared common motif in the agonist-induced phosphorylation of the receptor. As summarized in *Scheme 1*, both μ- and ∂-opioid receptors are phosphorylated at the Ser residue immediately after a Pro residue. Further, the second phosphorylation site is 4 residues upstream from the Pro. Interestingly, the Thr^{358} residue of the μ-opioid receptor does not have any acidic amino acid residue within the vicinity. In addition, Thr^{361} of the ∂-opioid receptor has a major role in the agonist-induced receptor phosphorylation, and itself is not the phosphorylation site. In the μ-opioid receptor sequence, a His residue is in the place of this Thr (*Scheme 1*). Thus, it is tempting to suggest that this Thr or His together with the Pro is a recognition motif for the kinases involved in agonist-induced phosphorylation of the opioid receptor. In the search of kinase recognition motifs within the literature, the current motif does not appear to fit any known kinases. Hence, it is possible that kinases other than GRK are involved in the phosphorylation of the opioid receptor. It is also possible that other enzymes, such as proline isomerases, participate in the GRK-mediated phosphorylation of the opioid receptor.

Phosphorylation of GPCR has been considered to be the key for receptor desensitization. If receptor desensitization, or uncoupling of the receptor from the effector is the key for opioid tolerance, then the blunting of the agonist-induced phosphorylation of opioid receptor should attenuate the receptor desensitization process, and possibly opioid tolerance. By identifying the agonist-induced phosphorylation sites, we could use homologous DNA recombination approach to generate mutant mice harboring the receptor phosphorylation minus mutant. If receptor phosphorylation is the mechanism for opioid tolerance, in these animals, morphine tolerance should be blunted. However, prior to these *in vivo* studies, a direct correlation between agonist-induced phosphorylation and receptor phosphorylation must be established. The exact phosphorylated residue(s) that participates in the receptor desensitization process needs to be identified. Unfortunately, the rapid desensitization of μ-opioid receptor was not observed when the agonist inhibition of adenylyl cyclase was used as readout of receptor activity. While the receptor phosphorylation occurred within minutes, the loss of response was observed to occur in the time course of hours (34). Hence, before we could identify which of the phosphorylation sites is critical for receptor desensitization, we need to explain for the failure to observe rapid desensitization of μ-opioid receptor. One possibility is the efficiency in which the receptor could regulate the adenylyl cyclase activity. The ability of ∂-opioid receptor to efficiently couple to the adenylyl cyclase has been well documented (41). A recent report has suggested that μ-opioid receptor desensitization appears to be related to the receptor content on the cell surface (42). Thus, the failure to correlate receptor desensitization and receptor phosphorylation could probably be due to the efficiency of coupling and the rapid recycling of the μ-opioid receptor. By carrying out FACS analyses in the presence of monensin, an antibiotic that would trap the internalized receptor within the endosomes, we observed that the rate of receptor disappearance was significantly faster than that observed in the absence of the antibiotics, suggesting the recycling of the μ-opioid receptor. However, monensin and brefeldin A together, which could block the golgi and endosomal trafficking of the receptor, did not enhance the rate of receptor desensitization (43). Only when the receptor level was decreased by 80% with β-FNA pretreatment did the rate of μ-opioid receptor desensitization increase in the HEK293 cells. Rapid desensitization of the μ-opioid receptor was observed only if the receptor density was at a very low level. Taking advantage of the relatively low level of μ-opioid receptor expressed in the SHSY5Y cells, ~49 fmole/mg-protein, we could demonstrate the rapid desensitization of the μ-opioid only if the recycling of the μ-opioid receptor in these cells was blocked by monensin and brefeldin A. Thus, the cell surface content and the recycling of the receptor play important roles in the rate of μ-opioid receptor desensitization.

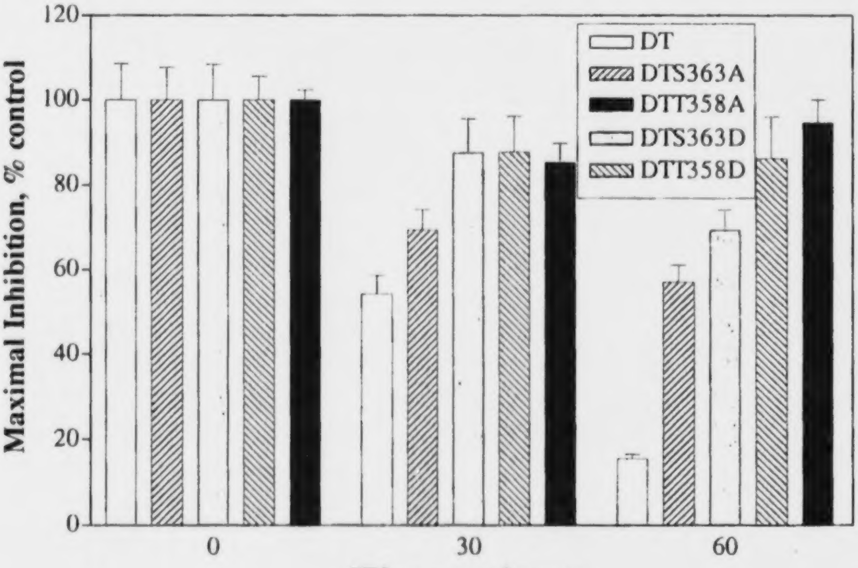
Scheme 1. Comparison of the agonist-induced phosphorylation sites of the μ- and δ-opioid receptors.

δ-receptor	-RVT*ACTPS*DGP-
μ-receptor	-QNT*REHPS*TAN-

Similar dependency of receptor desensitization rate on the level of cell surface receptor was observed also with the ∂-opioid receptor. By subcloning the cDNA of the ∂-opioid receptor or its mutants with the hemagglutinin epitope spliced at the N-terminus into the pINDsp1 vector containing the hybrid ecdysone response element (E/GRE) with multiple SP1 elements, when transfected into HEK 293 cells (EcR-293) expressing the heterotrimic ecdysone receptor (VgEcR) and the retinoid X receptor (RXR), the level of the ∂-opioid receptor responded to the concentration of ponasterone A present in the culture medium. When the ∂-opioid was over-expressed, >1 pmole/mg-protein, minimal receptor desensitization was observed after 1 hour of agonist treatment. Only when the receptor level was <100 fmole/mg-protein, was the rapid rate of ∂-opioid receptor desensitization then observed, correlating to the rate receptor phosphorylation (44). Though the ∂-opioid receptor was not known to recycle, the rate of desensitization, similar to that of μ-opioid receptor, was dependent on the level of cell surface receptor.

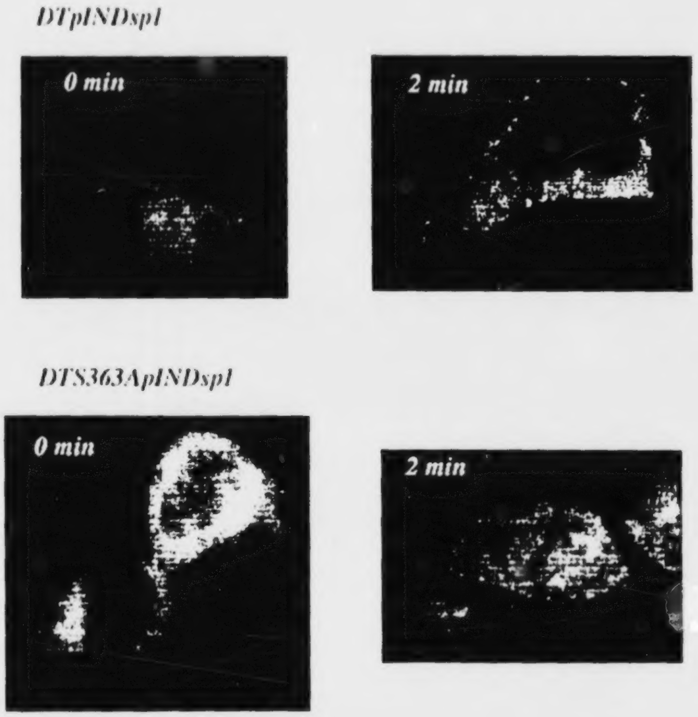
By controlling the receptor level on the cell surface, we could address the issue of the involvement of specific phosphorylated residue in the opioid receptor desensitization. The role of individual Ser/Thr residue was determined by the Ala or Asp receptor mutant. Mutation of the critical residue to Ala should blunt the phosphorylation and subsequently receptor phosphorylation. Mutation of the same critical residue to Asp should mimic the phosphorylated state, and hence potentiated the rate of receptor desensitization. However, when the Thr^{358} or Ser^{363} in the ∂-opioid receptor was mutated accordingly, a complicated picture emerged. As summarized in *Figure 2*, mutation of Ser^{363} to Ala, which completely blocked the agonist-induced receptor phosphorylation, did not completely blunt the DPDPE-induced receptor desensitization. Our other studies indicated that the remaining desensitization was due to the ability of agonist to induce internalization of the non-phosphorylated receptor (44). When the Thr^{358} residue was mutated to Ala, a better blockade of receptor desensitization was observed. Since in this mutant receptor, phosphorylation of the Ser^{363} residue still occurs, such data suggest that agonist-induced phosphorylation of the Thr^{358} is critical for agonist-induced receptor desensitization. The greater increase in the receptor desensitization magnitude was supported by the decrease in the rate of agonist-induced receptor internalization observed with this T358A mutant. However, when the same Thr^{358} was mutated to Asp, similar blockade of receptor desensitization was observed (*Figure 2*). If the phosphorylation of this residue is critical for the receptor desensitization, then the mutation to Asp, which mimics the phosphorylated state of the residue, should potentiate the receptor desensitization event, and should not block it. Similarly, the mutation of the Ser^{363} to Asp also prevented the DPDPE-induced desensitization of the receptor (*Figure 2*). Thus, the conversion of these two Ser/Thr residues to amino acids that mimic the phosphorylated state of the receptor did not enhance the rate of the rapid desensitization. Hence the agonist-induced phosphorylation of the receptor is not sufficient in triggering the receptor desensitization responses.

Figure 2. Ability of DPDPE to desensitize the wild-type and mutant ∂-opioid receptor stably expressed in EcR293 cells. Wild-type or mutant ∂-opioid receptor subcloned into pINDsp1 plasmids were stably expressed in EcR293 cells. The cells were cultured in the presence of 0.2 μM ponasterone A for 72 hours before treating with 1 μM DPDPE for the indicated time. The ability of 1 μM DPDPE to inhibit 10 μM forskolin-stimulated adenylyl cyclase activity was measured afterwards.



One possible reason for the ability of the agonist to desensitize the phosphorylation minus receptor mutant is that receptor phosphorylation only augments and is not a prerequisite for opioid receptor desensitization. If one examines the proposed mechanism for GPCR desensitization, it is the recruitment of arrestin to the receptor that terminates the receptor signaling. Phosphorylation of the receptor only increases the receptor's affinity for the arrestin molecule. In cellular environments in which the arrestin content is high, as in the case of HEK293 cells, even without receptor phosphorylation, there would be a sufficient amount of arrestin binding that could terminate the agonist-mediated signaling. If this is the case, then the phosphorylation minus mutant of the ∂-opioid receptor should interact with the arrestin molecule in the presence of agonist. We could demonstrate that this is the exact scenario by the use of ß-arrestin-GFP fusion protein constructs. By transfecting the EcR293 cells expressing the wild-type opioid receptor with the ß-arrestin-GFP fusion protein constructs, in the absence of DPDPE, the GFP fluorescence was uniformly distributed within the cytosol of the cells (*Figure 3*). Two minutes after the addition of 1 μM DPDPE, punctated structure of GFP fluorescence was observed at the plasma membrane, indicative of the recruitment of ß-arrestin-GFP proteins by the activated ∂-opioid receptor. Translocation of such punctated structure from plasma membrane to intracellular vesicles was not observed upon longer incubation with agonist. Possibly, these data suggest that the ß-arrestin molecule would not translocate with the ∂-opioid receptor to the endosomal compartments. Interestingly, when the EcR 293 cells expressing the S363A mutant of ∂-opioid receptor, the receptor mutant that was not phosphorylated in the presence of DPDPE, were treated with DPDPE for 2 minutes, similar punctated structure of GFP fluorescence was observed (*Figure 3*). Again, no translocation of such punctated fluorescence was observed with prolonged DPDPE treatment. Hence, regardless of receptor phosphorylation, ß-arrestin could interact with the ∂-opioid receptor upon agonist treatment, thus terminating the signaling processes.

Figure 3. *DPDPE-induced translocation of β-arrestin-GFP fusion protein to plasma membrane in EcR293 cells expressing either wild-type (DTpINDsp1) or S363A (DTS363ApINDsp1) ∂-opioid receptor.*



All the studies from our laboratory and others indicate that agonist activation results in the phosphorylation of the opioid receptor. Whether phosphorylation of the receptor is a prerequisite for the subsequent receptor desensitization has not been established. There are antidotal studies in which the receptor desensitization can be correlated with the receptor phosphorylation. However, there is also compelling evidence to suggest that receptor phosphorylation did not correlate with the blunting of the responses. With the identification of the agonist-induced phosphorylation sites, we were able to address this specific question of whether the phosphorylation of the Ser/Thr residues is required for the agonist-induced receptor desensitization. As indicated by our data, using adenylyl cyclase as the readout of opioid receptor activation, with the mutation of one or both of the phosphorylation sites on the opioid receptor, either ∂- or μ-opioid receptor, there is no complete blockade of the receptor desensitization. Since the regulation of the receptor level at the cell surface is a dynamic event, the mutation of the Ser/Thr residues could alter the cellular trafficking of the receptor and hence the activity of the agonist, and contributing to the degree of receptor desensitization. Even with the consideration of receptor trafficking, we were unable to identify an essential Ser/Thr residue that is responsible for the agonist-induced receptor desensitization. In a mutant devoid of measurable agonist-induced receptor phosphorylation, blunting of the response was observed after agonist pretreatment. Such results suggest that phosphorylation of the receptor is not essential for opioid agonist-induced receptor desensitization, at least in the cell model on which the studies were carried out. Such results do not suggest that receptor phosphorylation has no role in opioid receptor desensitization, or subsequently, opioid tolerance development. For the consequence of GPCR phosphorylation is the increase in the arrestin affinity and subsequent recruitment of arrestin molecule to the receptor's vicinity. Some GPCR, such as the opioid receptor, could interact with the arrestin molecule without being phosphorylated. As demonstrated by our arrestin-GFP translocation studies, agonist binding to the receptor is sufficient in recruiting the arrestin molecule, and subsequently receptor desensitization is observed. Hence, we would like to suggest that the recruitment and interaction of the arrestin molecule by the receptor is the essential step for opioid receptor desensitization. If this is the case, by designing drugs or agents that could interfere with the receptor-arrestin interaction, one could modulate the development of tolerance to morphine or other opioid agonists. This could be accomplished by elucidating the three-dimensional structure of the opioid receptor and arrestin interaction. It is toward this goal our current research effort in the determination of the molecular mechanism of opioid tolerance is focused.

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INTRODUCTION OF THE MARIAN W. FISCHMAN MEMORIAL AWARD

H. Kleber

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Description of Award

The Marian W. Fischman Annual Memorial Lecture at CPDD is designed for a female scientist who has made outstanding contributions in the field of substance abuse and combines this scientific ability with the generosity of spirit and willingness to help others characteristic of Marian. It honors the memory of this wonderful woman – her wisdom, intellect, and science; her joy in life; her warmth and love; and her bravery in fighting for her science and to advance the cause of women in science. The Award involves an Honorarium, Travel Expenses, Plaque, and Lecture at the annual meeting.

A few weeks before Marian died, I raised the possibility of such an award and she was enthusiastic about the idea but insisted it should be designated for a woman scientist. Marty Adler and the CPDD Board were kind enough to act quickly so that Marian knew before she died that the Award would be a reality. The gift from our family and the outpouring of generosity from her friends and colleagues made the award financially feasible.

As I learned first hand after Marian's death, there can be no love without loss, no joy without sorrow. While the past is irretrievable, the gift of memory enables us to recapture treasured moments so that this wonderful human being will remain with us and we eventually will be able to feel happy and fortunate to have shared her life.

Bio of Dr. Marian Fischman

Marian Rita Weinbaum was born in Queens, October 13, 1939, received her undergraduate education at Barnard College, a M.A. in Psychology from Columbia University, and her Ph.D. at the University of Chicago in 1972. Her dissertation on "Behavioral effects of methamphetamine in the Rhesus monkey" found persisting effects on decreased dopamine and serotonin in the brain, suggesting long-term damage. Carried out under the guidance of Bob Schuster and Lou Seiden, it opened up the study of long-term methamphetamine toxicity.

Following her Ph.D., she joined the Chicago faculty but soon switched her focus from nonhuman primates to humans and from methamphetamine to cocaine. There was an increasing use of cocaine among the "beautiful people" in the 1970's and cocaine was widely regarded as safe ("No more dangerous than skiing," Dr. Peter Bourne, President Carter's drug advisor, stated a few years later). However, some scientists were concerned so with encouragement from Bob Schuster and Norm Krasnegor at NIDA, Marian submitted her first cocaine grant and it was funded. Her research became the model for how behavioral pharmacology studies with drugs of abuse involving healthy, non-incarcerated human participants should be accomplished.

Marian's contributions in the area of cocaine research fall in two principal areas. The initial one was to develop techniques for studying the effects of cocaine in humans. Hers was the first laboratory in the United States, in the mid-70's at the University of Chicago, to be given permission to administer cocaine to human subjects and the first funded by the National Institute on Drug Abuse for that work. In spite of 25 years of safe and productive research with this technique at a number of universities, it remains controversial. Marian was an articulate spokesman for both the importance of this research and how to carry it out safely and ethically. She told an interviewer, "This research is badly needed. Not to do it would be unethical."

Marian's laboratory was the first to correlate behavioral and physiological effects with cocaine blood levels in humans, the first to combine these measures in carrying out parametric studies of drug interactions in humans, and the first to develop a laboratory model for studying stimulant self-administration by humans, vital to understanding the patterns of cocaine use and possible interventions. Her work was the most systematic human research on cocaine since Freud's "Uber Coca" in 1885. Her second focus was on a method for evaluating potential medications to treat stimulant abuse using a laboratory-based model. This approach provides a bridge between pre-clinical studies with non-humans and large-scale outpatient trials, contributing an improved basis for developing treatment interventions in substance abuse disorders. Her cocaine research led to her receiving in 1987 the first NIDA Merit

Award, which provided 10 years of funding for her research grant, "Cocaine Effects in Humans: Physiology and Behavior." Her cocaine work was carried out over these years with her longtime collaborator, Richard Foltin.

In 1984, Marian left Chicago to become Associate Professor at Johns Hopkins, joining their Division on Behavioral Biology. In addition to her career-defining studies on cocaine, her research expanded to address the behavioral pharmacology of smoked marijuana and then to study how workplace and other contingencies can alter drug self-administration. In 1990, she was appointed to Professor at Johns Hopkins and in 1992 she was appointed to Professor with tenure at Columbia.

In 1987, when I was still at Yale and she at Johns Hopkins, we began to see each other on a regular basis, commuting on weekends. In 1989, I moved to Washington to be the Deputy Director of the Office of National Drug Control Policy under Bill Bennett and President Bush and we were able to be together on a more regular basis. By late 1991, after weighing offers from a number of schools, we succumbed to the charms of Columbia and our friend Herb Pardes, the Dean and Chair of Psychiatry there. We moved to New York in 1992 after finding a wonderful apartment overlooking Central Park and near Lincoln Center. Together we founded and co-directed the Division on Substance Abuse at Columbia University and the New York State Psychiatric Institute and, in addition, she founded and directed the Substance Use Research Center, the centerpiece of which was a state-of-the-art residential research center Columbia built for her for over one million dollars.

Working together, we built from scratch one of the finest substance abuse research programs in the country. She was the brains, the soul, and truly the mother of the enterprise. Starting with just a few colleagues, she mentored a wonderful group of young scientists and we grew to over 100 staff. She possessed an uncommon ability to both conceptualize new approaches and to oversee their carrying out, the nuts and bolts of science. Her door was always open and on an average day 15-20 people, both from our division and elsewhere in Columbia, passed through with difficult or impossible questions. She was our sage and guru.

Her passion for science coupled with her love of mentoring brought a sense of teamwork to our division that inspired loyalty to a degree rarely found elsewhere. She played an integral mentorship role in the development of many scientists including at Columbia: Richard Foltin, Ned Nunes, Frances Levin, Suzette Evans, Sandra Comer, Margaret Haney, David McDowell, Eric Collins, Eric Rubin, Adam Bisaga, Maria Sullivan, Evaristo Akerele, Diana Martinez, and Carl Hart. All of them now have their own funding. She especially took pleasure in mentoring the young women on how to combine career and family. Along with other leaders in the field such as Nancy Mello, Chris-Ellyn Johanson, Maxine Stitzer, and Linda Dykstra, she fought for the scientific role of young women.

She was brave and outspoken about her ethical and scientific beliefs: whether defending before hostile audiences her JAMA article with Dorothy Hatsukami on why the crack vs. cocaine powder sentencing rules did not make sense scientifically or defending to hostile reporters her pioneering research.

While at Columbia, she not only focused on developing medications for cocaine abuse, but also, in addition, continued her marijuana research and moved into working with heroin addiction. Her research with Meg Haney demonstrated the presence of physical dependence on smoked marijuana with a clear-cut withdrawal syndrome, an idea still disputed by pro-marijuana groups. This led to research trying to develop medications to treat the withdrawal, which appears to be associated in many marijuana smokers with frequent relapse. Her heroin research with Sandra Comer provided new data on heroin use by the fast-growing routes of intranasal and smoking. Using a modification of her cocaine laboratory model, she published a number of important papers comparing the intravenous with these other routes and evaluated the effectiveness of several new medications including buprenorphine and a month-long formulation of depot naltrexone.

Dr. Fischman was an important figure on the national level as well, using her expertise to shape the field. She served on the NIH National Advisory Council on Drug Abuse, and the Board of Scientific Counselors of NIDA's Addiction Research Center. She was an Advisor to the World Health Organization, Division of Mental Health, and chaired the Clinical-Behavioral Initial Review Group of NIDA. She was a member of a number of Boards of Scientific Advisors, and consulted to many university research centers; served on two important committees of the Institute of Medicine/National Academy of Sciences; and served on the National Advisory Committee to set federal research priorities for the Office of AIDS Research. She was an editorial reviewer and on the editorial board of a number of distinguished scientific publications; was elected a fellow in the most prestigious organizations in her

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field (e.g., American Psychological Association, American College of Neuropsychopharmacology, College on Problems of Drug Dependence) and served them in a variety of capacities on boards and committees. She was a consultant to numerous federal commissions and councils, and was awarded the American Psychological Association Solvay Award for outstanding psychopharmacological research. She received frequent requests to speak and consult throughout the world and was to have given the Okey Memorial Lecture in London the week before her death. She served on the American Psychological Association's Task Force, which wrote "Ethics in Research with Human Participants," and continued her participation as an ad hoc advisor to that group. She is the author or coauthor of over 200 publications.

But our life was much more than our work. We played together, laughed together, traveled all over the world together. We especially loved to travel together. I remember her snorkeling at the Great Barrier Reef; walking with a koala bear on Kangaroo Island; bowing back to a bowing deer in Japan; treading the 2000 year old path of the Delphi priestess in Greece; enjoying the beauties of Positano; London; Paris; Florence; Istanbul; and on and on. She was an energetic, enthusiastic, and exciting travel companion. We enjoyed our children and grandchildren. As the numbers of the latter grew, they became our pride and joy. She was beloved not only by her children and grandchildren but by mine as well; thus together, 6 children and their spouses and 8 grandchildren blessed us.

She had a love of life that was infectious. Those who knew her and those who barely knew her returned the love. She died as she lived: with elegance, warmth, bravery, and wisdom. Even in the intensive care unit, the physicians remarked how her smile lit up the room when they entered. The internist who oversaw her care wrote, "Marian was one of the most unique patients I have ever had. I cannot think of anyone in my 33 years in medicine who faced death as bravely and with the dignity and control that Marian exhibited." People of different religions said prayers for her recovery all over the world.

To honor her many contributions, the College on Problems of Drug Dependence (CPDD) will present on an on-going basis the Marian W. Fischman Memorial Lectureship Award to an outstanding woman scientist in the drug abuse field at its yearly scientific meeting. Columbia University will also sponsor on an annual basis a Memorial Lectureship Award in Marian's honor for an outstanding scientist in the substance abuse field.

Bio of Dr. Chris-Ellyn Johanson

It is fitting that the first Marian W. Fischman Memorial Award at CPDD be given to Dr. Chris-Ellyn Johanson, a distinguished scientist and close colleague and friend of Marian. Dr. Chris-Ellyn Johanson earned her Ph.D. in biopsychology in 1972 from the University of Chicago where she first met Marian Fischman, a fellow graduate student. Both stayed on as faculty members with Dr. Fischman leaving in 1984 and Dr. Johanson in 1987. From then until 1992, Dr. Johanson was an Associate Professor at Uniformed Services University of the Health Sciences (USUHS), rising to rank of Professor in 1991. In 1992 she became Branch Chief of Etiology at the Addiction Research Center (ARC) in Baltimore. Finally, in 1995, Dr. Johanson joined the faculty of Psychiatry and Behavioral Neurosciences at Wayne State University, where she is currently professor and Associate Director of the Substance Abuse Research Division.

Dr. Johanson's primary interest during her early career was in determining the influence of a broad spectrum of behavioral and pharmacological variables on the relative reinforcing efficacy of drugs of abuse and the development of sensitive approaches for assessing abuse liability of psychoactive drugs in rhesus monkeys. While still continuing her animal research at the University of Chicago, she also developed a human psychopharmacology program investigating the reinforcing effects of psychomotor stimulants and benzodiazepines in normal humans. When Dr. Johanson moved to USUHS, human behavioral pharmacology became her primary interest. At the ARC, her research interests broadened to include the epidemiology of drug abuse and the development of paradigms that would foster a biobehavioral understanding of vulnerability to substance abuse.

Dr. Johanson has published more than 150 scientific articles, including several important reviews of the behavioral pharmacology of cocaine co-authored by Dr. Fischman. She was also the editor of *Drug and Alcohol Dependence* from 1986 to 1998 and helped make this the official journal of CPDD. She has attended the annual scientific meetings of the College (or Committee) on Problems of Drug Dependence regularly since 1971. That 1971 meeting was particularly memorable because Dr. Johanson was asked to leave the official CPDD hotel dining room at lunchtime because she was a female. Despite this rocky beginning, she has served on several committees of CPDD including the credentials, program nominating, publication, international and human research, and was appointed chair of the two latter committees. She served both on the Board of the Committee in the mid-80's and recently on the Board of Directors of the College.

Throughout her professional career, Chris-Ellyn and Marian had a strong bond both because of their shared research interests and also personally.

MARIAN W. FISCHMAN: RESEARCH LEGACY

C.E. Johanson
Fellow student, colleague, friend[*]

Wayne State University School of Medicine, Detroit, MI

MARIAN W. FISCHMAN
1939- 2001

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[*] This lecture is a highly personal account, subject to the usual distortions of memory and emotions. Marian's death has been painful to me in ways that I cannot express and I am not capable, thank heavens, of a totally neutral perspective on her research legacy. Marian did not work in a vacuum and without the influence and contributions of many others, some of whom paved the way for her, she could not have succeeded to the extent that she did. She would not have claimed otherwise. I have tried as much as possible to give credit where credit is due but for a variety of reasons, I may have failed. I apologize to any one who feels they have been slighted. I want to dedicate this lecture to Marian's children, Eric, Sharon and Amanda, whose contributions cannot be documented but who gave Marian peace and comfort (as well as the usual hassles and grief) throughout her career and who remain her most important contribution to this world.

It is a great honor to be the first recipient of the Marian W Fischman Memorial Lectureship, an honor both professionally and personally. Marian and I were friends and colleagues starting in 1968 and perhaps more than any one I was present to witness and appreciate almost her entire career. Although future awardees will make presentations about their own outstanding work, the intended purpose of this award, I thought it fitting as the first awardee to celebrate Marian's career instead of my own. Although many attendees at this CPDD meeting know Marian, at least by reputation, I doubt that any one has ever tried to review her research career as a whole with the intent of trying to pinpoint what characteristics made her a unique researcher, more than worthy of this special lectureship. In this regard, I want to comment on the issue that this award is intended for senior *women* scientists. Part of Marian's uniqueness stems from being a female in a male world. When she began her career, there were very few female role models. She entered graduate school pregnant with her third child and continued to play the traditional Jewish homemaker role. In the 60s, the decision to begin graduate school with these responsibilities took courage and it is this courage that is part of her endowment to the rest of us who struggle with maintaining a balanced life. Marian worked very hard and put in long hours but her personal life as a mother, spouse, and friend remained most important. She made compromises in both her professional and person life, some of which should not have been necessary had the world been more supportive of professional women. But she and others changed the face of the scientific workplace, imparting it with gentleness and grace but not weakness. This award is intended for women with the same courage and balance in their life who have demonstrated that they do not have to give up the qualities that distinguish them as women but at the same time can remain competitive in the demanding scientific world.

When Marian entered graduate school at the University of Chicago in 1968, she joined the laboratory of Robert McCleary and was interested in brain mechanisms underlying learning. McCleary was a traditional biopsychologist poking holes in brains and observing the behavioral outcome. Unfortunately, McCleary died when Marian was in her third year of graduate school and Marian had to seek a new home laboratory. I was in Bob Schuster's laboratory and knew he was about to receive a new grant that I thought would interest Marian. Bob and I argue whether Marian really had any other choices of laboratories because I credit him with being one of the few professors in the program willing to take on female graduate students, particularly ones with children. There were only two other female graduate student besides me in the program at that time (one being Linda Dykstra) and the program had never graduated a female student. Regardless of the truth, Marian and Bob made the right choice and all three of us benefited from Marian's presence, both scientifically and personally.

The project she attacked was tolerance to the behavioral effects of long-term, high-dose methamphetamine administration in rhesus monkeys. This grant was awarded early in the 1970s in response to the "speed" epidemic. As an aside, starting then and continuing throughout the remainder of her career, Marian was most interested in attacking issues with human relevance, one of the hallmarks of her research style. The monkeys in this study were administered methamphetamine eight times a day via an intravenous catheter and their behavioral performance, maintained by food under complex operant schedules, was measured. As they became tolerant to the behaviorally disruptive effects of a dose, it was increased until they were receiving 16 mg/kg/day for several months. Another aside: Marian was very well trained in operant behavior having received a masters from Columbia in behavioral analysis and having worked in the laboratory of a prominent behavioral analyst, Israel Goldiamond, before moving to Chicago. Ironically Goldiamond joined the University of Chicago faculty at the same time that Marian became a graduate student. Jim Appel, Daniel X. Freedman and the then graduate student Klaus Miczek were also there-it was an exciting place to be.

The methamphetamine study became Marian's dissertation. She demonstrated a profound level of tolerance that also appeared irreversible, staying evident for months (Fischman and Schuster 1977). Her completion of her dissertation research (in record time I might add-she still graduated after only 4 years in graduate school) required long hours because the monkeys required almost continual nursing care and the mounds of data that were produced required vigilance. This is another one of Marian's characteristics-always *look* at your data-not unique for successful scientists but which she taught unsparingly to her students (and one of its corollary's is "show me the data"). Although her research was behavioral in nature, Marian had not forgotten her interests in brain mechanisms. Perhaps because Bob also had an appointment in the Department of Pharmacology and because another pharmacology faculty member, Lewis Seiden, was a psychologist, i.e., also thought behavior was important, a collaboration was formed and Lew was given the monkeys' brains to analyze for the levels of catecholamines. What they found was astounding, a nearly 50% decrease in levels of dopamine even after several months since the last drug injection (Seiden *et al.*, 1975). This was one of the hallmark papers that launched the interest in stimulant neurotoxicity that continues today as a major research focus in psychopharmacology.

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But Marian was destined for a different career. It was 1975 and the abuse of cocaine was gaining momentum. But not since the time of Freud (1963) had any one given cocaine to humans in a scientific study. NIDA was interested in launching a research program and for reasons I cannot figure out, approached Bob Schuster. Bob had lots of experience in cocaine research but not using human participants. Bob turned to Marian (he was and remains a master of delegating responsibilities) who had no experience with cocaine or human research. A lot of behavioral pharmacologists at that time would have been too nervous to launch cocaine studies in humans but not Marian and Bob. There is a lesson here but I leave it to the reader to infer. The initial studies were carefully designed with the main emphasis being on safety and assessing the cardiovascular effects of iv cocaine (Fischman *et al.*,1976). Perhaps because she was not a physician, Marian was extremely cautious and concerned with the safety of the participants, both physical and psychological, as a primary issue. The physicians with whom she worked over the years I am sure would attest to this assertion. As a result, her collaborations with the medical world were positive experiences for both parties and have won the respect by physicians of non-physician clinical researchers from which many of us benefit. There are other noteworthy characteristics of this first study that deserve mention. First, few human laboratory studies with iv cocaine had been conducted and the whole intravenous methodology and testing protocol had to be developed. In seeking permission to conduct the studies from the FDA, Marian and Bob were required to recruit only participants who abused cocaine in a heroin-like pattern. They knew this was not appropriate but following her own principle, they set out to "show them the data." What this required was field work and again a lot of courage. Marian spent many evenings interviewing active drug users in their apartments and gathered enough accounts of their drug use patterns to convince the FDA and others that cocaine was taken in an intermittent, sporadic pattern including self-imposed days of abstinence, just like it is taken by monkeys in laboratory self-administration studies (Deneau *et al.*, 1969; Johanson *et al.*, 1976). In the first study conducted Marian tested a very wide range of doses of cocaine, from 4 to 32 mg/kg, did complete time course analyses, and used both a negative, placebo, and positive control, d-amphetamine. In addition, she included the evaluation of subjective effects in her studies, despite her own skepticism of their validity or even reliability for that matter. Perhaps because of this skepticism, she collected these data in as rigorous a manner as possible and treated the responses on the questionnaires as just another behavior, verbal in this case, that like other behaviors were susceptible to control by the consequences. Care was taken to avoid imparting expectations and studies were always double-blind and placebo controlled. Finally, Marian sought to establish a trusting relationship with her participants, treating them with dignity and respect. The protection of human subjects was not a much considered issue at that time (the Belmont Conference was just being published and there were no Institutional Review Boards) but already Marian was making contributions in this area. What I remember most about this first study was how excited we all were and also how much fun we were having, venturing into the whole new area of human behavioral pharmacology. Having fun is also an important legacy of Marian's although I cannot give her total credit for establishing this as an important ingredient in the scientific workplace. There were others of us who also thought fun was important in maintaining a sane workplace but Marian quickly picked up the attitude (this might not have been as easy as you might think-fun could also be viewed as frivolous, a characteristic no woman who aspired to becoming accepted as a professional could afford to be seen as having) and imparted it to all those with whom she came in contact over the remainder of her career.

Over her entire research career, Marian continued conducting human cocaine studies and it is for this body of research that she may be best known. The early studies included studies of duration of action with concurrent behavioral, cardiovascular, and pharmacokinetic evaluations, which provided the foundation for being able to conduct multiple dose studies safely and led to her seminal studies on acute tolerance (Fischman *et al.*, 1985). She initiated studies using smoked cocaine in response to the emergence of crack use (Foltin and Fischman 1991b). Again responding to important clinical issues, Marian was the first to evaluate the combined effects of cocaine with other drugs, those commonly taken with cocaine, alcohol and marijuana (Foltin and Fischman 1988; 1990). Safety again was a major issue but she also began to incorporate more behavioral measures of performance in these studies that fit more with her background and interests. One of the earliest studies in this regard evaluated the effects of cocaine on performance in sleep deprived individuals. There was a lot of lore about the ability of stimulants to improve performance but little supportive data (Weiss and Laties 1962). Fischman and Schuster (1980) demonstrated that while cocaine had only minimal effects on performance under baseline conditions, if individuals were sleep deprived and their performance was compromised compared to baseline, cocaine reversed these effects and restored performance. I highlight this study not only because I believe it is an important contribution but also because there is a related personal story that makes the point that research is about meeting challenges, serving as a good role model, and having fun. Marian and Bob were not sophisticated sleep researchers and were not really sure how to keep the participants awake during the 24 and especially 48 hr sleep deprivation condition. The only way they could really be sure they were awake was to keep them moving all night but they were reluctant to ask students or research assistants to tackle this job. So both Marian and Bob stayed up with each and every participant in that study. To keep them moving, they conducted architectural walking tours of the beautiful University of Chicago campus and downtown Chicago, which is filled with famous buildings by Sullivan, van der Rohe, and Wright and sculptures and murals by Picasso, Calder, Chagall, and many others. They had a lot of fun doing these tours and became more cultured at the same time.

Marian did not work in a vacuum. The rest of us in the laboratory (e.g., Bill Woolverton) were largely interested in the reinforcing effects of drugs of abuse and the environmental and pharmacological variables that modified drug self-administration. In our animal lab, cocaine was our drug of choice (e.g., Johanson and Schuster 1975). Investigators such as Mello, Mendelson, Griffiths, Bigelow, and Brady were conducting self-administration studies in humans with many drugs of abuse but not cocaine. The field was wide open and exciting and Marian's self-administration research eventually led to the development of a human model for assessing medications for the treatment of cocaine dependence.

Although measuring rates of responding maintained by drug administration contingent upon the response was the most prominent metric used to evaluate the reinforcing effects of drugs in animal models, such unlimited access was problematic in human studies because of the potential of excessive drug intake. So Marian, like many of us, looked for ways to minimize the amount of drug that was administered but at the same time, use drugs as reinforcers, i.e., allow self-administration. Choice procedures appeared to be one solution to this problem and were enjoying a popularity in animal studies. This approach allowed investigators not only to demonstrate that a drug was reinforcing if it was chosen more often than saline but also, because cocaine could be pitted against a variety of alternatives, such as other drugs, to assess relative reinforcing effects (Johanson and Schuster 1975). Marian modified this procedure and it is fair to say capitalized on this method for the remainder of her career. She carefully developed the parameters of the model and made sure she understood the variables that controlled preference. I will only review one study that I particularly like.

In this study (Foltin *et al.*,1992), participants were given a choice between smoked and intravenous cocaine. In a previous study by these investigators, the data had suggested that at equal plasma levels, the subjective effects of smoked cocaine were greater than those following iv cocaine. This suggestive evidence was followed by a self-administration study that more clearly demonstrated this to be true. As in the animal studies, the choice procedure consisted of both a sampling and choice phase. During sampling, participants were exposed to one iv dose and one smoked dose (both the doses and times between administrations were carefully chosen based upon her past research) and then were allowed to choose which route they preferred. At doses that produced similar acute subjective and cardiovascular effects, as in the previous study (systematic replication), smoked cocaine was preferred. As Marian continued to demonstrate in her research, subjective effects can easily be dissociated from reinforcing effects.

While Marian continued to do behavioral studies to refine the cocaine self-administration model (Ward *et al.*, 1997b) she also applied this model to the development of medications. I need to give some credit here to Herb Kleber, who was a pioneer in the development of medications, most especially desipramine, to treat cocaine dependence. Their personal relationship began in the late 1980s and coincidentally her first study on the effects of a medication on cocaine self-administration was published in 1990 and evaluated desipramine (Fischman *et al.*, 1990). This study made a very important conceptual contribution to the field. Although measures of certain subjective effects of drugs (e.g., MBG scale of the ARCI, drug liking, high) had been shown by many investigators to be highly correlated with their reinforcing effects measured by drug self-administration methods and even came to be used as surrogate measures (Foltin and Fischman 1991a; Schuster and Johanson 1988), Marian and other behavioral pharmacologists knew that reports of mood were not the same as drug-taking (even *saying* I want to take a drug is not the same as taking a drug). So in the desipramine study (Fischman *et al.*, 1990) both mood and drug-taking behavior were measured simultaneously and the results were provocative. Desipramine decreased a variety of cocaine's subjective effects, such as ratings of "I want cocaine", but had no effect on cocaine preference, i.e., they continued to take cocaine despite what they said. Over the next decade, Marian and her collaborators evaluated many potential medications and she promoted the now accepted tenet that it is far better to test a potential medication in a relatively inexpensive and rapid laboratory study than to immediately conduct an expensive clinical trial. But neither approach has yielded an efficacious medication and I am sure this was a great disappointment to Marian. But laboratory work of this kind is continuing and while she will not be here to receive the congratulations when a medication is found, many of us will remember that her work laid the foundations.

Although cocaine dominated Marian's research career, it did not completely define it. Early on she was interested in marijuana and in recent times, she utilized the methods she had developed with cocaine to study the reinforcing effects of heroin. Marian began marijuana studies when she joined the faculty at Johns Hopkins University in 1984.

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There was lots of drug lore about the effects of marijuana on behavior but very little had been proven under tightly controlled laboratory conditions. Did it cause the "munchies", an amotivational syndrome, and physical dependence? Marian translated these issues into operational definitions and conducted studies on food intake (Foltin *et al.*, 1986), performance (Foltin *et al.*, 1989), and behavioral changes following chronic marijuana administration (Haney *et al.*, 1999). These studies were conducted in an entirely new type of situation for Marian-in a programmed residential laboratory. Joe Brady had many years before designed and built a programmed residential laboratory that provided investigators with the ability to monitor and measure the behavior of individuals and groups continuously for 24 hr for weeks at a time using a networked computer system, i.e., avoiding direct participant-investigator interaction. Brady and his colleagues published several interesting studies (Brady *et al.*, 1974; Brady and Emurian 1978; Emurian *et al.*, 1983) but not with drugs. Marian saw this as another wide open field. The availability of the programmed residential laboratory represented a truly unique opportunity for a detailed assessment of the effects of drugs on behavior not unlike that afforded in animal studies. However, such studies require a dedicated and commitment of resources and time that many investigators would not have been willing to devote. Individuals are maintained in this environment continuously for weeks. Someone has to always be there and you can imagine how much data can be obtained. Marian and her co-workers, and in particular I would like to mention Richard Foltin, spent many days and nights over several weeks glued to monitors during each study. Even though she was head of the laboratory, Marian took her turn on the evening shifts, another example of her style of mentorship.

In order to examine "loss of goal-directed behavior" as described in a report published by the Indian Hemp Commission (1893) and since referred to as an "amotivational syndrome", Marian and her colleagues designed a protocol that required individuals to engage in a behavior that was low probability in order to earn time to engage in a recreational activity that was high probability, following the Premack principle (Foltin *et al.*, 1989; Premack 1965). No assumptions were made as to what constituted low and high probability recreational activities. These were determined individually for each participant by observing how they spent their time under conditions where no contingency was in effect, allowing the investigators to construct a time-based behavioral hierarchy and make exquisite use of systematic replication. During the contingency phase, individuals had to spend four times as much time, relative to the no contingency phase, engaged in the lowest probability behavior (the instrumental behavior) in order to earn time to engage in their highest probability behavior (the contingent behavior). Imagine how difficult this study was to conduct as it required constant vigilance of each individual. But the results demonstrated that marijuana did decrease rates of the instrumental behaviors in 12 of the 15 participants but had little effect on rates of contingent behaviors. The effects were not huge but they were significant and without the development of a sensitive baseline and the use of motivational conditions, might not have been observable.

It probably is no surprise, however, that Marian was most interested in the reinforcing effects of marijuana and how these could be modified by behavioral contingencies. In a study by Ward *et al.*, (1997a), also conducted in the residential programmed environment now located at Columbia, the ability of a money alternative to alter marijuana self-administration was evaluated under conditions where performance requirements to earn the chosen option (marijuana or money) were imposed and these requirements changed for money across different sessions. This study clearly demonstrated that the ability of the money alternative to decrease marijuana preference was lawfully related to how much work was required to obtain the money. The more costly in terms of work output the money, the more likely that marijuana was preferred. However, actual performance was not affected by which option was chosen even though participants had received an administration of marijuana prior to the work phase. Further, the subjective effects of marijuana clearly indicated that individuals were intoxicated when working on the performance tasks but this did not predict choice or influence performance. So what is important about this study in terms of characterizing the Marian's contributions? First, it is in reality a very complicated study (it has to be read carefully to fully appreciate this) yet very lawful results emerged. Second, the design allowed Marian to make comparisons to her previous studies using a type of systematic replication. The procedures were similar to previous studies but not identical but still looked at the effects of contingencies, performance, THC content, and choice. Third, she continued to measure both choice behavior and subjective effects and once again demonstrated that they can be dissociated. Finally, she continued to demonstrate that although individuals may be seen as dependent, implying a lack of control over drug-taking, in fact, their behavior is clearly dependent upon and controlled by contingencies.

In recent years, Marian and her colleagues developed a model for evaluating the reinforcing effects of heroin in order to use this model for testing medications. Obviously these studies are similar to the cocaine studies but required an adjustment because of the necessity of keeping individuals maintained on an opiate to avoid the confound of abstinence effects. She continued to use the choice procedure but modified it to be more sensitive by incorporating a progressive ratio schedule. The results demonstrated lawful relationships between pharmacological (dose of heroin) and environmental (amount of money alternative) variables. As dose increased, preference increased but if the amount of alternative money was increased, the increase was not as great. Although self-administration studies with medications have not yet been published, these were underway at the time of Marian's death. What is important about switching to heroin as the target drug is that efficacious medications already exist for the treatment of heroin dependence, unlike cocaine dependence. I am sure this must have excited Marian because the validity of the self-administration model could be tested more rigorously.

While I have barely touched the surface of Marian's contributions, I want to end with a couple of studies that were favorites of both of us because they showed so clearly the malleability of a drug's reinforcing effects. Both of these studies, one with amphetamine (Comer *et al.*, 1996) and one with alprazolam (Haney *et al.*, 1997), were conducted on the residential unit with non drug-dependent volunteers. They used a choice paradigm where participants sampled drug and placebo during the initial sessions followed by choice sessions, a procedure that has almost become classic. However, when they sampled drug and placebo they were required to perform on tasks. Following the task completion, they received money contingent upon their performance. Or so they thought. In fact, the experimenters "rigged" the feedback to suggest either that the participant had done worse or better than average. In one phase of the study, doing worse was associated with the active drug and doing better with placebo. The "contingencies" were reversed for the next phase. When participants had been told they had done worse after active drug, their choice of active drug drastically decreased compared to when doing better was associated with active drug. Again, environmental contingencies altered the reinforcing effects of the drugs and in a direction that has clinical implications.

Throughout this presentation, I have tried to characterize the contributions of Marian by describing studies illustrating her approach. Marian's contributions in many ways were characteristic of an era where there was tremendous progress in the development of human behavioral pharmacology. These studies were successful to a large extent because they translated methods that had been successful in animal drug studies to humans, retaining as much rigor as possible. The manipulation of parameters to verify that lawful effects could be generated in humans and the use of systematic replication (Sidman 1960) were cornerstones. Verbal behavior was an important outcome measure utilized throughout, but as Marian continued to emphasize, verbal behavior, just like any other behavior, could be controlled by the contingencies. Although Marian considered her work basic, i.e., just like preclinical studies, she managed to ask and answer important clinical questions. The consistent demonstration that drug-taking behavior was under contingency control even in so-called dependent individuals was an extremely important finding with far-reaching implications. Finally, it is important to point out that Marian gave a great deal of thought to ethical issues and was often consulted by her colleagues on these matters (Fischman and Johanson 1998). She treated the volunteers in her studies with dignity and respect and fervently defended their rights, even the right to consent to take drugs when properly informed of the risks.

Luckily, Marian was also an excellent teacher and mentor to many junior colleagues so human behavioral pharmacology will continue to thrive even in her absence. I believe she was particularly proud of the group of investigators that she worked with at Columbia. While working with others, she always did her share and the fact that she was a laboratory head didn't mean she wasn't available to do what needed to be done at the moment. She was demanding of her students and junior colleagues work but she modeled these behaviors she demanded. She was serious about her science but she loved life and thought all of life should be fun, including research. Marian had extraordinary courage and she was proud to be a female with all the uniqueness that that conveys.

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SYMPOSIUM I

IS DOPAMINE THE ANSWER? EVIDENCE FOR THE IMPORTANCE OF OTHER SYSTEMS IN THE REINFORCING/NEUROCHEMICAL EFFECTS OF PSYCHOSTIMULANTS

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For over 20 years, the focus of studies examining the neurochemical and behavioral effects of cocaine and other psychostimulant drugs has been on dopamine. Cocaine binds to the dopamine transporter and inhibits dopamine uptake, and many studies have shown that dopamine plays an important role in the reinforcing and behavioral effects of cocaine. A number of studies have shown that there are some effects of cocaine on dopamine receptors, dopamine levels, and the dopamine transporter. These neurochemical studies have not, however, been able to fully account for the altered behavioral effects of cocaine following chronic cocaine administration, suggesting that other neurochemical components are necessary for the reinforcing effects (and hence the abuse) of cocaine. This symposium focused on neurotransmitter systems, other than dopaminergic, that have a major role in the effects of psychostimulants. The roles of neuronal nitric oxide, serotonin, norepinephrine, and opioid peptides were discussed. The data showed that there are interactions between multiple systems and that these interactions are important factors in the effects of abused drugs that should be considered in the process of developing new treatments for stimulant abuse.

THE IMPORTANCE OF NEURONAL NITRIC OXIDE IN MEDIATING THE EFFECTS OF PSYCHOSTIMULANTS

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We investigated the role of neuronal nitric oxide synthase (nNOS) in a) the psychomotor stimulating effects of cocaine, methamphetamine (METH) and methylphenidate (MPD), b) the rewarding effects of psychostimulants, and c) the neurotoxicity induced by METH. The nNOS inhibitor, 7-nitroindazole (7-NI) blocked the induction and expression of sensitization to the locomotor stimulating effects of cocaine, METH and a low dose of MPD. In addition, mice deficient of the nNOS gene (nNOS knockout mice) were resistant to cocaine-induced locomotor sensitization. The role of nNOS in the rewarding effects of cocaine and other abused substances (e.g., alcohol and nicotine) is suggested by the following observations. First, 7-NI blocked cocaine-, ethanol- and nicotine-induced conditioned place preference (CPP) but not LiCl-induced conditioned place aversion in mice, suggesting the specific role of NO in mediating reward processing. Second, nNOS KO mice were resistant to cocaine-induced CPP. The involvement of nNOS in METH-induced dopaminergic neurotoxicity is supported by the following findings: First, several nNOS inhibitors such as 7-NI, 3-Br-7-NI and S-methylthiocitrulline (SMTC) attenuated METH-induced depletion of dopaminergic markers with no significant effect on METH-induced hyperthermia. Second, nNOS KO mice were resistant to METH-induced dopaminergic neurotoxicity. In all the behavioral paradigms tested and in the neurochemical studies there was a good correlation between the pharmacological blockade of nNOS and the deletion of the nNOS gene. Therefore, nNOS has an important role in mediating both the rewarding and neurotoxic effects of psychostimulants. Further studies are necessary to determine whether selective nNOS inhibitors may be useful therapeutics for the management of addiction to psychostimulants.

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COCAINE SELF-ADMINISTRATION IN DOPAMINE AND NOREPINEPHRINE TRANSPORTER KNOCKOUT MICE

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A large body of evidence supports the hypothesis that the reinforcing effects of cocaine depend on the ability of this drug to block the dopamine transporter (DAT), thereby increasing dopamine (DA) extracellular concentration within the mesocorticolimbic system (Wise, 1984). However, the fact that cocaine similarly binds to the serotonin and norepinephrine transporters (SERT and NET, respectively) raises the possibility that modulation of mesocorticolimbic dopaminergic transmission might be achieved through alternate pathways. Indeed, either serotonin-uptake inhibitors or norepinephrine uptake inhibitors have been shown to modulate the reinforcing and subjective effects of cocaine (Peltier and Schenk, 1993; Tanda *et al.*, 1997; Walsh and Cunningham, 1997). In addition, cocaine has been shown to be self-administered when directly injected in the prefrontal cortex of rats (Goeders and Smith, 1983).

The successful disruption of the genes coding for the DAT (Giros *et al.*, 1996) or for the NET (Xu *et al.*, 2000), offered ideal tools to determine the extent of the participation of these transporters and monoaminergic systems in the reinforcing effects of cocaine. With this purpose, intravenous (i.v.) cocaine self-administration was evaluated in DAT and in NET knockout mice.

DAT knockout mice self-administered cocaine within the same dose range and pattern than wild type controls (Rocha *et al.*, 1998). On the other hand, the dose response for cocaine self-administration in NET knockout mice was significantly shifted to the right (Rocha *et al.*, 1999). These results suggest that the reinforcing potency of cocaine was maintained in the absence of the DAT but decreased in the absence of the NET.

Because the NET in the prefrontal cortex is known to clear DA from the synapses (Carboni *et al.*, 1990; Gresch *et al.*, 1995), it is possible that in DAT knockout mice this pathway was still assuring increase in the dopaminergic transmission in presence of cocaine. We tested this hypothesis by evaluating the uptake of DA into synaptosomes prepared from caudate and frontal cortex of DAT knockout, NET knockout and wild type control mice. The data showed that in DAT knockout mice, DA uptake in frontal cortex occurs at the same rate than in wild type mice, while it did not occur in the caudate. The opposite was observed in NET knockout mice, where DA uptake occurred normally in caudate but not in frontal cortex (Moron *et al.*, 2002).

Taken together, the data do not discard the role of mesocorticolimbic DA transmission in the reinforcing effects of cocaine, but rather suggest that NET uptake of DA in the prefrontal cortex is a major pathway implicated in the reinforcing effects of cocaine.

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THE IMPORTANCE OF SEROTONIN IN MEDIATING THE EFFECTS OF COCAINE

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Neuropharmacological research has identified convergent roles of dopamine (DA) and serotonin (5-HT) systems in the behavioral effects of cocaine. In particular, the 5-HT$_2$ receptors have been characterized to control dopamine (DA) mesocorticolimbic circuits thought to be critical in the elicitation of behaviors evoked by psychostimulants. Two important DA mesocorticolimbic pathways originate in the ventral tegmental area (VTA) and terminate in the nucleus accumbens (NAc) and prefrontal cortex (PFC); both 5-HT$_{2A}$ receptors (5-HT$_{2A}$R) and 5-HT$_{2C}$R have been localized to these nuclei. Recent studies have shown that systemic administration of 5-HT$_{2A}$R-preferring agonists (e.g., 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; DOI) enhanced the locomotor and discriminative stimulus effects of cocaine while 5-HT$_{2A}$R antagonists (e.g., M100907) blocked the hyperactive and discriminative stimulus effects of cocaine (Filip and Cunningham, submitted; Fletcher *et al.*, 2002; McMahon and Cunningham, 2001; Munzar *et al.*, 2002). Fletcher and colleagues also reported the ability of 5-HT$_{2A}$R blockade to decrease cocaine-primed reinstatement of cocaine self-administration after extinction (Fletcher *et al.*, 2002). These data suggest that the "priming" injection triggers a 5-HT$_{2A}$R-dependent stimulus profile that promotes continued drug-seeking and suggests the potential therapeutic utility of a 5-HT$_{2A}$R antagonist as an abstinence enhancer. Some DA neurons contain 5-HT$_{2A}$R (Doherty and Pickel, 2000) and neurochemical studies suggest that 5-HT$_{2A}$R may play a facilitatory role on DA synthesis and/or release under conditions of DA stimulation (De Deurwaerdere and Spampinato, 1999; Schmidt *et al.*, 1992); thus, indirect stimulation of these 5-HT$_{2A}$R following cocaine-induced 5-HT reuptake inhibition appears to contribute to the behavioral profile presented by cocaine.

The behavioral effects of cocaine are also under the influence of the 5-HT$_{2C}$R. The majority of the data collected to date suggests that 5-HT$_{2C}$R agonists suppress and 5-HT$_{2C}$R antagonists enhance the stimulus, reinforcing and "priming" effects of cocaine (Filip and Cunningham, submitted; Fletcher *et al.*, 2002; Grottick *et al.*, 2000). In contrast to this consistent picture, cocaine-induced hyperactivity is biphasically affected by the 5-HT$_{2C}$R agonists and antagonists tested to date (Filip and Cunningham, submitted; Fletcher *et al.*, 2002; McCreary *et al.*, 1999). These data support a generally inhibitory role for 5-HT$_{2C}$R in the control of cocaine behaviors and one which is oppositional to that described for 5-HT$_{2A}$R (above). A number of electrophysiological and neurochemical studies support the concept that the 5-HT$_{2C}$R controls DA neurotransmission in mesocorticolimbic circuits underlying the behavioral effects of cocaine (De Deurwaerdere and Spampinato, 1999; Di Matteo *et al.*, 2002).

To map the neural sites of action for 5-HT$_2$R to control cocaine-induced behaviors, intracranial microinjection studies have been employed to deliver selective 5-HT$_{2A}$R and 5-HT$_{2C}$R agonists or antagonists into the VTA, NAc or PFC. Intra-VTA microinfusion of the selective 5-HT$_{2A}$R antagonist M100907 blocked expression of cocaine-evoked hyperactivity but intra-NAc infusion of M100907 had no effect (McMahon *et al.*, 2001). On the other hand, intra-NAc infusion of the 5-HT$_{2C}$R antagonist RS 102221 dose-dependently suppressed the hyperlocomotive (McMahon *et al.*, 2001) and stimulus effects of systemically-administered cocaine (Filip and Cunningham, 2002). In contrast, RS 102221 did not alter cocaine-induced hyperactivity upon infusion into the VTA (McMahon *et al.*, 2001). Taken together, these findings suggest that separate populations of 5-HT$_2$R resident within the VTA vs. NAc differentially function to control the mesoaccumbens pathway. Such differential regulation of this circuit may help to clarify the observed, mixed influence of systemically administered non-selective 5-HT$_2$R antagonists in previous studies of the behavioral effects of cocaine (see Filip and Cunningham, 2002, for references). Perhaps the outcome of systemic, pharmacological experiments with 5-HT$_{2A}$R and 5-HT$_{2C}$R ligands depends in part on the functional balance between 5-HT$_{2A}$R and 5-HT$_{2C}$R in the mesocorticolimbic pathway. We have recently shown that microinfusion of a 5-HT$_{2C}$R agonist or antagonist into the rat PFC actually reduced or enhanced, respectively, the locomotor and discriminative behaviors of cocaine (Filip and Cunningham, 2000). These findings might help explain the discrepancy between systemic and intracranial application of 5-HT$_{2C}$R ligands such that the net effect of simultaneous activation (or blockade) of 5-HT$_{2C}$R in NAc and PFC following systemic administration of a 5-HT$_{2C}$R ligand may be due to a potentially oppositional contribution of distally-located 5-HT$_{2C}$R to the ultimate behavioral outcome of systemic drug studies.

In summary, the research abstracted here reinforces the hypothesis that 5-HT$_{2A}$R and 5-HT$_{2C}$R contribute distinctively to the regulatory neurochemistry of the mesocorticolimbic circuits important to the full expression of behaviors evoked by cocaine.

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THE ROLE OF OPIOID PEPTIDES IN COCAINE ABUSE

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Acute elevation of dopamine levels following cocaine administration is associated with euphoria, positive mood state, motor activation, and accelerated mental activity. However, it is clear that repeated, long-term cocaine use results not only in euphoria, but also in negative mood states, behavioral sensitization, psychosis, anxiety, aggression and anhedonia. This wide range of cocaine effects are presumably not all mediated by dopamine. It is proposed that increased levels of dopamine induced by cocaine leads to a cascade of cellular (and structural) events some of which initiates compensational mechanisms to renormalize the dopamine tone. These compensatory neuroadaptations may themselves result in impaired behaviors such as depression and behavioral sensitization seen after long-term cocaine use.

The striatum is a complex brain structure important for dopamine-mediated behaviors including drug reward, motivation, and motor function. It is well documented that the primary neurons in the striatum are medium spiny GABAergic cells that differentially express the opioid neuropeptides dynorphin and enkephalin and constitute the output pathways. Dorsal striatal neurons expressing prodynorphin (and dopamine D1 receptors) innervate mainly the substantia nigra; neurons expressing enkephalin (and dopamine D2 receptors) primarily innervate the external globus pallidus. The brains of human stimulant users are characterized by an upregulation of the prodynorphin mRNA levels with a greater effect in the limbic-related patch compartment of the dorsal striatum. Non-human primate studies have recently been used to reveal the time course of the effects of cocaine self-administration on prodynorphin mRNA expression. The results show that the patch compartment is more affected by cocaine after both initial (5 days self-administration) and long-term (100 days) cocaine self-administration. In addition to elevation of the prodynorphin gene, human (as well as monkey) subjects with a history of cocaine use show a profound down regulation of the striatal proenkephalin gene expression. The imbalance of the prodynorphin (increased) and proenkephalin (reduced) striatal output pathways as a consequence of cocaine use would predict a number of neurochemical and behavioral adaptations. First, these opioid striatal alterations would lead to a subsequent negative feedback of dopamine transmission to counteract the increase dopamine tone induced by the acute cocaine use. Dynorphin peptides are preferentially ligands for kappa opioid receptors, whereas enkephalins are ligands at mu (and delta) receptors. Stimulation of kappa receptors decreases dopamine release, whereas stimulation of mu receptors increases dopamine release. Human cocaine users show elevation of kappa with reduced mu opioid receptors. Thus, increased dynorphin levels concomitant with decreased enkephalin would predict a subsequent reduction of dopamine release. The opioid gene alterations observed in human cocaine users could also account for the appearance of negative mood states apparent with repeated cocaine use. Increased dynorphin/kappa is associated with dysphoria, whereas the opposite (euphoria) is evident for enkephalin/mu. Increased striatal prodynorphin mRNA expression has been observed in human suicide subjects with a similar anatomical pattern observed in human cocaine users with alterations specific to the patch compartment. Based on basal ganglia circuitry, the prodynorphin alterations in human cocaine users would also be expected to predict increased motor sensitization to cocaine use based on potentiation of striatonigral (prodynorphin), but reduction of the striatopallidal (proenkephalin) pathways. Recently, it was found that prodynorphin mRNA expression levels in the striatum in hemi-parkinsonian monkeys are in fact positively correlated ($r=0.76$; $p < 0.01$) to the animal's motor response to dopamine agonists.

In summary, opioid neuropeptide alterations that are prominent in the brains of human cocaine users may be compensatory to the initial alterations of increased dopamine. Overall, the potentiation of monoamines by cocaine initiates a sequence of events that triggers long-term neuroadaptation of striatal neuronal populations. Specific neuroadaptations evident in primate striatal output neuronal populations include upregulation of prodynorphin with a concomitant down-regulation of proenkephalin. Such alterations might account for some of the behavioral neuroadaptations characteristic of long-term repeated cocaine administration, e.g., negative mood state and behavioral sensitization.

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BIDIRECTIONAL INTERACTIONS BETWEEN DOPAMINE AND OPIOID RECEPTORS: IMPLICATIONS FOR THE REGULATION OF COCAINE ABUSE

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Kappa-opioid receptor agonists block the behavioral effects of cocaine, both acutely and long-term. Days after the last of several injections of a kappa-opioid receptor agonist, the ability of cocaine to stimulate locomotor activity is still markedly reduced. This suggests that significant alterations in brain neurochemistry have occurred. Our previous studies suggest that dopaminergic changes alone cannot account for the decreased behavioral effects. Thus, it appears that other neurochemical systems are playing an important role in these long-term decreases in cocaine-stimulated activity. There are reciprocal interactions between cocaine and kappa-opioid receptors. Chronic cocaine increases kappa-opioid receptors predominantly in serotonin rich brain regions, and the upregulation is not produced by selective dopamine uptake inhibitors. Together, these findings suggest that the bi-directional interactions between cocaine and kappa-opioid receptors are mediated by neurochemical systems other than dopamine.

We investigated the role of serotonin in mediating the interactions between kappa-opioid receptors and cocaine. Depletion of serotonin by parachloroamphetamine (PCA) had no effect on the ability of U-69593 alone to decrease locomotor activity. Thus, the behavioral effects of U-69593 alone are not dependent upon serotonin. Following PCA treatment, however, there were significant increases in locomotor activity in rats challenged with an injection of cocaine regardless of whether they had been pretreated with U-69593 or vehicle. Further, activity levels in these two groups of rats were not different from one another. This is in contrast to an animal with intact serotonin, where U-69593 pretreatment markedly blocks the behavioral effects of cocaine. Thus, serotonin depletion prevents the blockade of the locomotor-activating effects of cocaine by U-69593. These findings suggest that serotonin plays an important role in mediating the effects of kappa-opioid agonists on the behavioral response to cocaine. In addition, the effects of U-69593 on prodynorphin mRNA levels were blocked by PCA treatment. These findings suggest that serotonin plays an important role in the effects of kappa-opioid agonists, and in the interaction between the kappa-opioid system and cocaine.

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SYMPOSIUM II

SUBSTANCE ABUSE, IMMUNOMODULATION AND INFECTIONS

H. Friedman and T. K. Eisenstein, Chairpersons

OVERVIEW

This symposium focused on affects of several drugs of abuse on immunity and susceptibility to infections. It is now widely recognized that drugs of abuse alter the immune response and their use is often associated with increased susceptibility to infectious diseases, especially by opportunistic intracellular microbes common in patients with AIDS. In recent years, much attention has been focused on the accumulating new information concerning the effects of recreational drugs of abuse on modulation of immune responses. This symposium focused attention on several drugs of abuse known to affect immunity, including their role in altering susceptibility to infections. Dr. Thomas Rogers from Temple University reviewed data on the influence of opioids widely studied in regard to effects not only on the neurologic, but also the immune system, especially as related to AIDS. He presented new data from his laboratory on the interaction of opioids on chemokine receptors by a process of heterologous desensitization. Dr. Robert Donahoe from Emory University then reviewed the literature on opioid addiction and susceptibility to HIV and progression to AIDS, and presented new data from his laboratory on effects of chronic morphine use on progression of simian immunodeficiency virus in a simian model. The next speaker, Dr. Guy Cabral from the Medical College of Virginia, described new findings showing that cannabinoids, especially tetrahydrocannabinol, the major psychoactive component of marijuana, alters the susceptibility of microglia to infection with a parasite. The next speaker, Dr. Susan Pross from the University of South Florida, summarized data from newer studies showing that nicotine, now classified as an addictive drug, blocks apoptosis of immune cells, both by a specific receptor as well as a non-receptor mediated mechanism. The final speaker, Dr. Philip Peterson from the University of Minnesota, summarized the symposium and discussed how drugs of abuse increase or inhibit replication of HIV in CD4 lymphocytes, depending on dose and time of exposure.

BIDIRECTIONAL HETEROLOGOUS DESENSITIZATION BETWEEN CHEMOKINE AND OPIOID RECEPTORS

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The opioid and chemokine receptors are members of the Gi protein-linked seven-transmembrane receptor family. These receptors are expressed by cells of the immune system, and most notably, by leukocytes which mediate the inflammatory response. Moreover, the ligands for these G protein-coupled receptors (GPCR) are known to be co-expressed at sites of inflammation. The function of GPCRs can be regulated at the protein level through the processes of either homologous or heterologous desensitization. Recent evidence has shown that the mu- and delta-opioid receptors can mediate heterologous desensitization of the chemokine receptors CCR1, CCR2, CXCR1 and CXCR2 (Grimm *et al.*, 1998; Liu *et al.*, 1992). These studies showed that pretreatment with opioids, including morphine, heroin, met-enkephalin (ME), the more selective mu-agonist [D-ala^2, *N*-Me-Phe^4, Gly-ol^5]enkephalin (DAMGO), or the selective delta-agonist [D-Pen^2, D-Pen^5]enkephalin (DPDPE) leads to the inhibition of chemotactic responses of leukocytes to complement-derived chemotactic factors (Liu *et al.*, 1992) and to the chemokines CCL3 (formerly macrophage inflammatory protein [MIP-1α]), CCL5 (formerly regulated on activation normal T cell expressed and secreted [RANTES]), CCL2 (formerly monocyte chemotactic protein [MCP-1]) and CXCL8 (formerly IL-8) (Grimm *et al.*, 1998). In the present report we first sought to examine the capacity of mu- and delta-opioids to modulate the function of CCR5 and CXCR4, the two chemokine receptors which serve as the major HIV co-receptors. In addition, we considered the possibility that the cross-desensitization between the chemokine and opioid receptors may be bi-directional. Therefore, we hypothesized that prior exposure to chemokines might result in heterologous desensitization of opioid receptors, a process with physiological relevance given the significant accumulation of both opioids and chemokines in most inflammatory response states.

We initially assessed cross-talk between opioid and chemokine receptors using primary human peripheral blood monocytes. We found that pre-treatment with either met-enkephalin, DPDPE, or DAMGO resulted in a failure of

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the monocytes to carry out a chemotactic response to the CCR1/5 ligand RANTES (CCL5). Because RANTES is a ligand for both CCR1 and CCR5, we wished to clarify further whether mu- or delta-opioids would induce desensitization of a CCR5 response in CHO cells transfected with CCR5 and the mu-opioid receptor (MOR). Using these cells, we found that both mu- or delta-opioids induce desensitization of CCR5 at opioid concentrations as low as 1-10 nM. In contrast, both mu- and delta-opioids failed to induce detectable desensitization of CXCR4 in monocytes or a number of other monocyte and lymphocyte cell lines. These results suggest that mu- or delta-opioids induce selective cross-desensitization of CCR5 but not CXCR4.

We considered the possibility that the desensitization of CCR5 responses may be associated with the down-regulation (internalization) of the CCR5 receptor. Experiments were carried out by flow cytometry with both monocytes and CHO cells transfected with both CCR5 and MOR. Our results show that mu-opioid administration fails to induce any detectable loss of CCR5 membrane expression. Additional experiments carried out by both laser-scanning confocal fluorescence microscopy and by radio-labeled binding analysis also showed that mu-opioid treatment fails to induce internalization of CCR5.

We wished to determine the effect of mu-opioid-induced heterologous desensitization on susceptibility to HIV infection using both peripheral blood mononuclear cells and monocyte-derived macrophages. Cells were first desensitized by treatment with 10 nM DAMGO, the cells were infected with either X4 or R5 strains of HIV-1 for 1 hr, washed, and the replication of HIV was determined by determination of the release of HIV p24. Results show that _-opioid administration results in a significant inhibition of infection by R5, but not X4, strains of HIV-1. This is consistent with the observation, described above, that CCR5, but not CXCR4, is desensitized by mu- or delta-opioids.

In studies to assess the bi-directional nature of the cross-talk between opioid and chemokine receptors, we attempted to determine the effect of a number of chemokines on the response of both mu- and delta-opioid receptors. Using a number of diverse cell populations, we found that administration of CCR2, CCR5, CCR7 and CXCR4 receptor ligands induced desensitization of both mu- and delta-opioid receptors. In contrast, ligands for CXCR1 and CXCR2 failed to induce desensitization of either mu- or delta-opioid receptors, and this is consistent with the selective nature of the cross-talk between these GPCR families.

Finally, we have also evaluated the possibility that activation of chemokine receptors in vivo may desensitize brain _-opioid receptor function, and interfere with the perception of pain in the CNS. These in vivo experiments were carried out by administration of either CCR5 or CXCR4 chemokine ligands into the periaqueductal grey matter (PAG). This was followed 30 min later by administration of DAMGO to test the functional activity of the _-opioid receptor. Our results showed that chemokine pre-treatment blocked the ability of the _-opioid receptor to mediate normal analgesia activity.

In conclusion, the inactivation of CCR5 function by both mu-and delta-opioid agonists has implications for our understanding of the inflammatory response. The CCR5 receptor is expressed by T cells, NK cells, and cells of the monocyte/macrophage lineage, and elevated levels of the ligands for this receptor (CCL3, CCL4 and CCL5) are well established components of the inflammatory response. Moreover, the desensitization of the opioid receptors by chemokines, suggests that the production of chemokines associated with episodes of inflammation and tissue injury in the brain would result in altered neuronal function, and specifically, in reduced opioid receptor-mediated analgesia. It should be appreciated that exaggerated pain (hyperalgesia) occurs as a part of inflammatory stress reactions, and this pain response is a condition that often occurs with systemic inflammatory "flu-like" reactions. The possibility that a reduction in analgesia may contribute to the pain in the periphery associated with inflammatory disease states including rheumatoid arthritis, dental caries, and certain infectious diseases, should be investigated further. Our studies support the hypothesis that the heterologous-desensitization of the mu-opioid receptor induced by chemokines may provide a basis for the hyperalgesia associated with inflammatory reactions in general.

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OPIATES AND SIMIAN AIDS

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The longstanding controversy (1) about whether opiates themselves affect progression of AIDS continues unabated. This issue relates, of course, to the obvious connection between intravenous drug abuse (IDA) and AIDS. For the last several years, the incidence of AIDS in ID abusers has held steady at its peak of about 35% of current AIDS cases. Whether opiate exposure influences virus expression and host defenses against the virus, however, remain key unanswered issues.

Controversy in this aspect comes from conflicting reports from animal models, and from clinical/epidemiological and in vitro studies, that have indicated that opiates variably have no effect on AIDS progression, exacerbatory effects, and retarding effects. There is no easy answer in this matter because of the complexities of the biological systems involved in assessing opiate effects (1). However, the data that we have obtained in a monkey study with opiate-dependent monkeys infected with the simian AIDS virus, SIVsmm9, have led to a hypothesis that helps explain conflict in this regard.

In a pilot study (2), we found that 6 opiate-dependent rhesus monkeys were 'protected' against AIDS onset relative to two separate sets of historic controls (total n = 28). We found also that virus expression could be transiently induced in these monkeys after they reached a quiescent stage of infection, by episodes of naloxone-precipitated opiate-withdrawal. Such withdrawal is extremely stressful. Therefore, it is important that variable stress levels are well-documented moderators of AIDS progression and that lentiviruses are known to be induced under stress conditions. Since viral load and AIDS progression rate are interdependent, our data suggest that well-maintained homeostatic-balancing opiate-dependencies slow AIDS progression by reducing stress and viral load, while an opposing effect occurs when stress is exacerbated by opiate withdrawal. This idea is stated as a homeostatic hypothesis of opiate affects on AIDS progression, dependent on the pharmacological circumstances of opiate exposure.

Given the pilot nature of our initial study and the controversies surrounding its conclusions, we have embarked on a well-controlled monkey study aimed at testing our homeostatic hypothesis in a statistically meaningful way. Using the same dependency and infection parameters as before, we have made 19 male rhesus monkeys (3-4 yr-old) dependent on morphine injections delivered four times a day (every 6 hr; 2-3 mg/kg, im-sc), while injecting a control group of 18 monkeys with proportional volumes of saline. Two weeks after initiation of these reagent injections, all monkeys were infected with 10,000 TCID50 of SIVsmm9. Baseline data for a number of immune and other physiologic parameters were obtained 2 wk before these procedures started, and data have been collected on a regular basis ever since using a longitudinal study design.

The data from this study are yet preliminary. More time is needed to ascertain the impact of our procedures on AIDS progression during the homeostatic phase of study, with the expected outcome being that AIDS progression rate will be slowed by our well-maintained opiate dependency. After we reach an endpoint of assessment based on survival analyses, we will then proceed to the second phase of study wherein our counter-hypothesis will be explored, that is, does opiate withdrawal and stress exacerbate viral load (with the presumption that this will accelerate AIDS progression)?

The preliminary data from the current study support the notion of homeostatic protection against increasing viral load and AIDS progression. If these data hold, as we expect, we will have obtained the first solid, direct evidence that opiate exposure modulates progression of AIDS. Such data represent a refutation of prevailing epidemiological thought, that opiates have 'no' influence on AIDS progression rate. Furthermore, such data will mean that beneficial treatment of AIDS victims may derive from the principles embodied in the homeostatic hypothesis. That is, AIDS therapies may be directed through intervention with the endogenous opioid axis, or other axes connecting the worsening of AIDS to stress. Such data will also be relevant in treating addiction in the context of AIDS. For example addicts with AIDS may benefit from the homeostatic generating effects of methadone maintenance and other similar therapies.

It remains to be explained why much epidemiological data (1,3) tend largely to find no evidence of opiate's influence on AIDS progression. It may be that epidemiological assessments have mostly missed the impact of counteractive effects of opiates and other drugs found in an addiction milieu, which along with other factors may bias subject selection. From our current data, it is logical to conclude that if one subgroup of addict is in uncompensated high stress due to opiate withdrawal and other milieu factors, the outcome would be that AIDS in this group would have accelerated progression. On the other hand, addicts whose dependencies are well maintained would be expected to experience low stress and slowed progression to AIDS—an outcome found to prevail for heroin addicts in two epidemiological studies (4,5). If this interpretation is valid, then for epidemiological assessments to be inclusive and truly representative, they must, at the very least, subgroup addicts on the basis of the stability of their opiate-dependency.

In conclusion, with hard-fast evidence that opiate's affect AIDS progression, the onus of rectifying these data with prevailing epidemiological thought that opiates have 'no' effects on AIDS progression shifts back to the clinic. Under current circumstances, it seems unwarranted and potentially harmful to proper AIDS management and to the public health to espouse a lack of opiate effects on AIDS progression.

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CANNABINOID-MEDIATED EXACERBATION OF BRAIN INFECTION BY OPPORTUNISTIC AMEBAE

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Recent reports indicate a higher frequency of brain infections with opportunistic amebae among individuals whose immune systems are compromised, including AIDS patients and individuals undergoing immune suppressive therapies (Martinez and Visvesvara 1997; Marciano-Cabral *et al.*, 2000). Principal among these amebae are members of the genus *Acanthamoeba* which cause Granulomatous Amebic Encephalitis (GAE), a chronic debilitating disease of the central nervous system (Martinez and Visvesvara 1997). *Acanthamoebae* also have been associated with cutaneous lesions and sinusitis in AIDS patients and in other immune compromised individuals (Martinez and Janitschke 1985; Friedland *et al.*, 1992; May *et al.*, 1992; Helton *et al.*, 1993; Torno *et al.*, 2000). *Acanthamoebae* are distributed world-wide and have been isolated from freshwater samples, seawater, swimming pools, physiotherapy units, tap water, bottled water, dust, soil samples, air, air-conditioners, dialysis units, dental treatment units, contact-lenses, and contact-lens solutions (Rodriguez-Zaragoza 1994). The life cycle of these amebae consists of trophozoite and cyst stages. The trophozoite is the feeding and dividing stage. Trophozoites ingest bacteria as a food source but also may harbor bacteria and serve as vectors for these microbes (Rowbotham

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1980, 1986; Barker and Brown 1994). The cyst, which contains a double-walled structure, forms in response to adverse environmental stimuli and is resistant to chemicals and therapeutic drugs. While the trophozoite constitutes the infective stage, both trophozoites and cysts are found in infected tissues. Because cysts also may harbor bacteria, they may sequester bacteria from anti-microbial immune responses as well as from the action of anti-microbial agents.

Marijuana has been approved in a number of states as a therapeutic agent to relieve pain and as an anti-emetic in cancer patients, for enhancing appetite in AIDS patients, and for treatment of individuals suffering from glaucoma. However, marijuana also has been reported to be immune suppressive and to alter resistance to infection with bacteria, viruses, and other pathogens in a variety of *in vitro* and *in vivo* models (Cabral and Dove Pettit 1998). The majority of the immune suppressive properties of marijuana has been attributed to its major psychoactive component, delta-9-tetrahydrocannabinol (THC) (Klein *et al.*, 1998; Cabral and Dove Pettit 1998).The pathogenesis of Granulomatous Amebic Encephalitis is poorly understood and given the increased numbers of immune suppressed individuals who may be exposed to this opportunistic pathogen, there is a need to understand the role of immune suppressive drugs, such as THC, on susceptibility to infection. Indeed, one of the earliest reported cases of amebic encephalitis was in a drug addict from Texas who died after 18 days of neurological symptoms with meningoencephalitis (Patras and Andujar 1966). We have utilized a murine model ($B_6C_3F_1$ mice) of amebic encephalitis to investigate the effect of THC on the outcome of infection with *Acanthamoeba castellanii*, an agent which targets the central nervous system. THC was shown to exacerbate *Acanthamoeba*-induced neuropathogenesis. Mice receiving an intraperitoneal treatment regimen of THC and exposed to a lethal-dose twenty (i.e.,1 LD_{20}) of *Acanthamoeba castellanii* intranasally exhibited drug dose-related higher mortalities from infection with *Acanthamoeba* than similarly infected vehicle controls. A 13% mortality rate was recorded for infected animals treated with vehicle. In contrast, animals receiving 10 mg/kg, 25 mg/kg, or 80 mg/kg THC exhibited approximately 33%, 40%, and 50% mortalities, respectively. *Acanthamoebae* were isolated from brain tissue as well as from lungs of all animals that died indicating colonization at multiple sites (Marciano-Cabral *et al.*, 2001).

The greater severity of disease for mice treated with THC occurred concurrently with dysfunction in responsiveness of macrophage-like cells to brain infection. Staining of paired serial sections of brain from infected mice treated with THC with anti-Mac-1 or anti-*Acanthamoeba* antibodies demonstrated that Mac-1+ cells were abundant in focal areas of infected brain tissue for vehicle-treated animals. Concurrent staining with the microglial marker isolectin B_4 confirmed these cells as microglia. Few amebae were co-localized in focal areas replete with Mac-1+ cells. In contrast, foci in brain tissue from infected, THC-treated mice were replete with amebae but contained few Mac-1+ cells. This paucity of Mac-1+ cells at focal sites of *Acanthamoeba* infection suggests that these immune cells either do not migrate to infected areas or, alternatively, are targeted by the *Acanthamoeba* and destroyed.

In order to extend these studies on effects of THC on macrophage-like cell activity, *in vitro* experiments were performed using purified neonatal rat cerebral cortex microglia or murine peritoneal macrophages. Both microglia and peritoneal macrophages when subjected to activation with immune modulators such as bacterial lipopolysaccharide (LPS) exhibited cell contact-dependent cytotoxicity against *Acanthamoeba* trophozoites. Activated microglia and peritoneal macrophages also phagocytosed *Acanthamoeba* when in the cyst form. In contrast, unactivated microglia or activated microglia pre-treated with THC (10^{-5} M and 10^{-6} M) rather than exhibiting anti-*Acanthamoeba* activity were, in turn, targeted by the amebae. Amebae destroyed the macrophage-like cells by contact-dependent killing which involved both necrosis and apoptosis. In addition, THC treatment of microglia altered the profile of inducible cytokine expression elicited in response to *Acanthamoeba*. THC treatment (10^{-5} M -10^{-7} M) of microglia resulted in a dose-related decrease in inducible mRNA expression for IL-1α, IL-6, and TNF-α. Concomitant with effecting decreases in the inducible expression of mRNAs for these pro-inflammatory cytokines, THC treatment resulted in augmentation of the expression of mRNA for the anti-inflammatory cytokine TGF-β which was elicited in response to co-culture with *Acanthamoeba* (10 microglia per ameba). The THC-induced augmentation in gene expression for the anti-inflammatory cytokine TGF-β may articulate a mode by which this cannabinoid alters macrophage-like cell responsiveness to *Acanthamoeba*.

The role of cannabinoid receptors in the THC-mediated inhibition of microglial responsiveness to *Acanthamoeba* remains to be defined. Neonatal rat microglia, similar to peritoneal macrophages, undergo a multi-step process to full activation in response to multiple signals (Carlisle *et al.*, 2002). "Resting" microglia assume a "responsive" state in response to chemokines and other stimuli. "Responsive" microglia exhibit characteristic functional features, including migration toward sites of infection and phagocytosis of "foreign" particulates. "Responsive" microglia , in turn, can be "primed" to express Class II molecules of the Major Histocompatability Complex (MHC) and to present antigenic peptides in the context of these heterodimeric molecules. Finally, "primed" microglia can by driven to "full activation" in response to a second signal such as bacterial lipopolysaccharide. "Fully activated" microglia exhibited inducible expression of pro-inflammatory cytokines, including IL-1α, IL-6, and TNF-α. We have shown that microglia express CB_1 and CB_2 receptors differentially in relation to cell activation state (Waksman *et al.*, 1998; Carlisle *et al.*, 2002). While expression for the CB_1 remained unaffected for any state of activation, that for the CB_2 was maximal for microglia when in the "responsive" and "primed" states. In contrast, minimal levels of CB_2 were recorded for microglia when in the "resting" and "fully activated" states. The presence of high levels of CB_2 receptors on microglia when in the "responsive" and "primed" state suggests that the functional activities attributed to microglia when in these states of activation may be the most sensitive to the action of cannabinoids. Microglia *in vitro* exhibited an augmentation in the levels of mRNA for the CB_2 in response to co-culture with *Acanthamoeba*. A similar augmentation in the expression of mRNA for the CB_2 was observed from homogenates of brain obtained from mice infected intranasally with *Acanthamoeba*. These observations are consistent with the data indicating that THC alters microglial responsiveness to *Acanthamoeba* infection.

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NICOTINE – INDUCED IMMUNOMODULATION

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Nicotine, the small organic alkaloid synthesized by tobacco plants, has long been recognized as the addictive component of tobacco. Many researchers have demonstrated that nicotine itself has biologically relevant properties in addition to being addictive. For example, nicotine has a history of use as an insecticide, since it is a potent ganglionic blocking agent. In terms of human health, it is thought that nicotine contributes to the alterations in the cardiovascular, pulmonary, gastrointestinal, urogenital, hepatic and nervous systems that are related to tobacco smoking. The extent of these effects of nicotine is exquisitely sensitive to the doses used and to the timing of nicotine exposure, making it critical to consider these variables when reviewing reports in the field. Nicotine's action can be considered indirect, when the role of nicotine on the hypothalmic-pituitary-adrenal axis and resultant secretion of epinephrine from the adrenal glands must be considered during *in vivo* experiments, and direct, as when the effect of nicotine is assessed on a given cell population *in vitro*. Understanding how nicotine acts on specific cells of the immune system is critical to appreciating how nicotine may affect immunity in general.

Nicotine's alkaline and lipophilic properties allow it to be readily transported across cell surfaces, but its primary effects are thought to be receptor mediated. Nicotinic acetylcholine receptors (nAChRs) are found on cells of both the central and peripheral nervous systems in addition to many other cells throughout the body, explaining the action of nicotine on a wide variety of biological actions. These nicotinic receptors are pentameric transmembrane ion channels that open when an agonist, usually acetylcholine, is bound, allowing sodium and calcium ions to cross into cells and then activating second messenger pathways. The primary way that the body is exposed to nicotine is via tobacco smoke, with cigarettes containing approximately 1.5 to 2.5 mg of nicotine. Smoking one cigarette per day can lead to blood concentrations of approximately 20 to 50 ng per ml and plasma levels of nicotine can reach as high as 700 ng per ml in heavy smokers. Nicotine can be delivered to the body by methods independent from smoking, including smokeless tobacco as well as patches, liquids and pills used for therapeutic purposes. The therapeutic use of nicotine is for smoking cessation therapy; however, other purported helpful effects of nicotine are to increase memory in Alzheimer's patients, to reduce tics in Tourette's syndrome, and to aid patients with inflammatory bowel disease. Since there is a growing use of nicotine in terms of therapeutic potential, an understanding of how it impacts other body systems, including immunity, is critical.

It is only in recent years that nicotine has been investigated in terms of its immunomodulatory capabilities. The nAChRs have been found on many immune cells, providing additional biological relevance to pursuing this direction of investigation. Since the specific nicotinic receptor subunits on immune cells have not been definitively delineated, especially as they may relate to immune cell subpopulations, this is an important area of current investigation. In addition to interest in the nicotinic receptor, research into the role of nicotine on immunity has been pursued through functional studies. In this regard, it has been demonstrated that exposure to nicotine alters calcium-dependent signal transduction pathways in immune cells. Furthermore, nicotine induced modulation of cytokine production by many cell types, including lymphocytes and macrophages, has been reported by our laboratory as well as by others. Since cytokines are critical in communication between cells, alteration in production of these proteins by nicotine may change how the body reacts to infections or to tumors. Specifically, nicotine has been shown to decrease the production of certain inflammatory cytokines such as TNF-alpha in murine splenic macrophages, as assessed by studies where fluorescent-labeled antibodies are bound to the proteins being analyzed (ELISA). Nicotine has also been shown to alter the production of cytokines produced by T lymphocytes. Our laboratory has shown a decrease in IL-10, a cytokine produced by T cells of the Th2 subpopulation, when murine splenocytes were studied. Importantly, the literature shows many conflicts in terms of the role of nicotine on cytokine production and these disparities can be accounted for, in part, by the concentrations of nicotine used, the timing of drug exposure, and the cells analyzed. In addition, the nicotinic receptors are rapidly desensitized, making these studies challenging to perform. We are currently expanding our investigation on cytokine production to looking at additional cytokines and using more cell types, in order to better characterize this action of nicotine. Some of the techniques used for this direction include, in addition to ELISA, the study of expression of relevant cytokine mRNA by the use of RT-PCR, and when quantitation is needed, real-time RT-PCR.

Recent studies from our laboratory have focused on the role of nicotine and apoptosis (programmed cell death) in lymphocytes as well as in endothelial cells. Apoptosis is a critical mechanism for maintaining homeostasis of cell numbers and thus this process functions in many biological systems, including the immune system. Modulations in the process of apoptosis would conceivably alter tumor growth, and impact on inflammation, relevant to autoimmunity and atherosclerosis. In experiments from our laboratory, cells (murine splenocytes or human coronary artery endothelial cells) were stimulated with agents such as dexamethasone or TNF-alpha in order to induce apoptosis. Apoptosis was determined in several ways, including measurement of active caspase-3, an enzyme that increases during apoptosis, as well as by DNA fragmentation, TUNEL assay, to visualize the alteration of DNA during apoptosis. Cells were either untreated, treated with either nicotine alone (either 0.01 μg/ml or 1μg/ml), or with nicotine in combination with the apoptosis inducers. It was found that nicotine tended to decrease the basal levels of apoptosis occurring in the untreated cells and to significantly decrease the levels of apoptosis in cells exposed to dexamethasone or TNF-alpha. This decrease in apoptosis was shown to be receptor mediated, since d-tubocurarine chloride, a general nicotinic receptor antagonist, was able to block the action of nicotine in these studies. Additional experimentation into the role of nicotine in apoptosis are being pursued in our laboratory, using receptor antagonists that are specific for individual nicotinic receptor subunits in order to more finely dissect this issue.

The hypothesis that nicotine is involved in alteration of immune responses is being pursued on different levels – both *in vivo* and *in vitro* studies have provided information showing an impact of nicotine on immunity. The question of course is whether the differences noted in the experimental settings represent areas of potential clinical impact. Since nicotine is being used by many people via tobacco products, and also as pills and patches for therapies, there is interest by the scientific community in terms of these studies. A greater understanding of the impact of nicotine on immune parameters is clearly needed to maintain an educated balance for the constructive use of nicotine.

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DRUGS OF ABUSE, IMMUNOMODULATION & AIDS

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A lethal effect of opium given to a prisoner with quartran fever (i.e., probable malaria) was witnessed over four centuries ago. However, the advent of injection drug use (IDU) in the late 19th century heralded major infectious disease complications of opiate use. These infections included an increased incidence of pneumonia, tuberculosis, hepatitis, and infective endocarditis (Risdahl *et al.*, 1996). In the past two decades, the association of IDU with acquisition of HIV-1 infection has had an even more dramatic impact on the lives of heroin-dependent individuals. While it was quickly realized that sharing of needles contaminated with HIV-1 was the most important reason for their increased risk of AIDS, a report in 1979 that human T lymphocytes possessed receptors for morphine (Wybran *et al.*, 1979) raised the possibility that opiates could also promote the pathogenesis of HIV-1 by impairing the immune system.

The so-called "cofactor hypothesis," i.e., that opiates and other substances of abuse which adversely affect immunity foster development of AIDS, has been intensively investigated during the past 15 years. From these studies, it is now clear that many psychoactive agents can impact negatively on the immune system, either indirectly via central nervous system (CNS)-mediated pathways or by direct effects on cells of the immune system (Eisenstein and Hilburger 1998). In the case of opiates, lymphocytes and macrophages have been shown to express receptors for all major classes of opioids (μ, κ, and δ) (Sharp *et al.*,1998). Also, a large number of experimental animal models of infection have shown that opiate administration increases infectious disease-related morbidity and mortality (Risdahl *et al.*,1996). Nevertheless, primate models of simian immunodeficiency virus infection and epidemiologic data in IDU subjects have yielded conflicting results regarding the role of substances of abuse in the pathogenesis of HIV-1 infection (Donahoe and Vlahov 1998).

Pharmacologic factors have been proposed as one potential explanation for the contradictory findings regarding the impact of drug-induced immunodeficiency in SIV models and in HIV-1-infected drug-dependent patients (Donahoe and Vlahov 1998). To evaluate the influence of such factors, our laboratory has used two cell culture models that are highly relevant to HIV-1 pathogenesis: HIV-1 replication and gp120-induced neuronal apoptosis. Although the caveat must be stressed that in vitro findings may not reflect the more complicated circumstances of drug-dependent HIV-1-infected subjects, the underlying thesis of our work has been that results with cell culture models can provide insights into this complexity and may yield new treatment strategies.

In recent studies, we have used purified $CD4^+$ lymphocytes obtained from activated human peripheral blood mononuclear cells to assess the effects of varying the concentration and time of exposure to morphine on HIV-1 expression. Results of these studies have revealed that morphine's effect on viral expression is both concentration- and time-dependent. While 24 hours of pre-treatment of $CD4^+$ cells with morphine potentiates viral expression, exposure of $CD4^+$ cells to this opiate for 30 minutes prior to HIV-1 expression markedly inhibits viral replication. An inhibitory effect on viral expression has also been observed with the synthetic cannabinoid WIN 55,212-2, both in cultures of purified $CD4^+$ lymphocyte cultures and in human microglial cells. Also, WIN 55,212-2 treatment was found to block the potentiating effect of 24-hour of morphine pre-treatment on HIV-1 expression. Concentration and time studies of the κ-opioid receptor ligand (KOR) U50,488 have revealed a consistent inhibitory effect of this opioid on viral expression in $CD4^+$ cells, monocyte-derived macrophages, and microglial cell cultures. Finally, the opiate antagonist naltrexone has been found to have no effect on HIV-1 expression by itself; however, naltrexone significantly increases the antiretroviral activity of standard antiviral drugs in $CD4^+$ lymphocyte cultures. Taken together, these in vitro studies have demonstrated profound effects of varying the concentration and time of exposure of cells to an opiate on viral expression, as well as opposite and interacting effects of other psychopharmacologic agents and antiretroviral drugs on this phenomenon in vitro.

Clinical and experimental evidence points to a pivotal role of activated brain macrophages and of neuronal apoptosis in HIV-1-associated dementia (HAD). We have used primary human fetal neuronal cell culture models to evaluate the effects of opioids on HIV-1- related brain disease. In recent studies, morphine has been shown to potentiate neuronal apoptosis induced by the HIV-1 protein gp120, supporting the notion that opiates promote development of HAD. In contrast to morphine, the KOR ligand U50,488 was found to inhibit neuronal apoptosis induced by supernatants from HIV-1-infected microglial cells. The mechanism for this neuroprotective effect appears to involve suppression of microglial cell production of quinolinic acid, an NMDA receptor ligand. Also, U50,488 has been shown to markedly suppress the production of monocyte chemotactic protein (MCP)-1 by astrocytes stimulated with the HIV-1 protein Tat. Due to its ability to recruit monocytes into the brain, MCP-1 has been implicated in HAD. Thus, findings from studies of cell culture models that simulate HAD suggest that while μ-opioid receptor agonists enhance, KOR agonists may inhibit HIV-1-mediated brain disease.

In summary, the results of studies with our cell culture models have demonstrated the important influence of pharmacologic factors, such as, timing, concentration and drug-drug interactions on the outcome of processes that are highly relevant to HIV-1 pathogenesis. These studies may shed light on the conflicting results from experimental models and epidemiologic studies of the "cofactor hypothesis" that substances of abuse foster progression of HIV-1 infection. Also, it is proposed that cell culture models may serve in the discovery of new treatments of HIV-1-infected patients.

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SYMPOSIUM III: WHAT ARE THEY THINKING? THE MEDIATING ROLE OF PARENTAL COGNITIONS IN THE PARENTING PROCESSES OF DRUG-DEPENDENT MOTHERS AND FATHERS

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Overview

Researchers of parenting and addiction have identified multiple global risk factors (e.g., poverty, childhood trauma, psychopathology) beyond drug use alone that are associated with maladaptive parenting and child outcomes in families affected by parental drug-dependence. Little is understood, though, about the mechanisms of influence underlying these associations. Ecological models of parenting suggest that individual parenting characteristics (e.g., personality, psychopathology) mediate associations between global risk and parenting behavior. Attachment theory further suggests that internal models of parenting function as "the higher process of integration and control of behavior systems." Preliminary research has shown that drug-dependent parents' internal conceptions of parenting are often impoverished, laden with negative affect, and characterized by anxieties unique to parental addiction. In this symposium, we examined drug-dependent parents' internal conceptions of parenting as determinants of parenting behavior and/or child outcomes, and as potential mediators of global risk in parenting processes. Specifically, we examined the mediating roles of four cognitive representations: (1) perceptions of emotional support, (2) parental role strain, (3) reflective functioning, and (4) psychological representations of fathering. Examining the role of these internal conceptions has important implications for understanding mechanisms of change in maladaptive parenting and for the development of empirically based parenting treatment interventions.

EARLY BONDING, PSYCHOPATHOLOGY AND PERCEIVED EMOTIONAL SUPPORT: USING AN ATTACHMENT THEORY FRAMEWORK TO UNDERSTAND HOW RISK FACTORS WORK TOGETHER TO INFLUENCE PARENTING

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Background: Drug-dependent mothers are at risk for parenting deficits in multiple domains, including perception of and responsiveness to children's emotional cues, consistency of approaches to discipline, and knowledge of child development. Multiple psychosocial risk factors associated with maternal addiction, including disruptions in families of origin, co-morbid psychopathology, and impoverished interpersonal relationships, have been identified as correlates of maladaptive parenting, and in some cases, as better predictors of maladaptive parenting among drug-dependent mothers than drug abuse alone. Nonetheless, few theoretically driven studies have examined the underlying mechanisms linking psychosocial risk factors with drug-dependent mothers' maladaptive parenting. Attachment theory offers a useful framework for doing so. Based on the theoretical work of John Bowlby (1982), attachment theory stresses the importance of *mental models of relationship* that form during early caregiving relationships and influence subsequent psychosocial development. According to attachment theory, when early caregivers are unable to accurately perceive and sensitively respond to their children's emotional cues, a child is likely to develop mental representations of the caregiver as unavailable or inconsistent, and to sustain similar mental representations of others as unavailable during adulthood. The failure of the early attachment relationship to provide a feeling of security also influences the child's capacity for affect regulation, which may later manifest as psychopathology during adulthood. As parents, individuals whose mental representations of relationship during adulthood are impoverished are also likely to characterize their caregiving relationship with their child as unsatisfying and problematic.

Hypotheses: In this study, we were interested in testing two hypotheses derived from attachment theory in a sample of drug-dependent, methadone-maintained mothers. First, we were interested in determining if two indices of maternal psychopathology (depression and drug use severity) function as a *proxies* for or *symptoms* of a more global disturbance in perceived availability of support and nurture in current relationships. Second, we were interested in determining if mothers' perceptions of support and nurture in current relationships mediate associations between their early bonding experience and their current perceptions of their relationships with their children.

Assessments: Maternal psychopathology was assessed with the Beck Depression Inventory (BDI: Beck & Beck, 1972) and the Drug Use Severity Composite score from the Addiction Severity Index (ASI: McLellan *et al.*, 1992). Given the preliminary nature of the study, we used simple measures to assess mothers' perceptions of early bonding experience, current relationships, and caregiving relationships with children. The quality of early caregiving relationships was assessed using the Maternal Care (degree of warmth and affection in maternal relationship) and Overprotection (degree of intrusion and control in maternal relationship) subscales from the Parental Bonding Instrument (PBI: Parker, 1989). Current availability of support and nurture was assessed with the Family and Peer Support subscales from the Procidano Social Support Scale (PSSS: Procidano & Heller, 1983). Mothers' perceptions of parenting problems were assessed using the Adaptability (degree of flexibility in relationship with children) and Cohesion (degree of emotional bonding in relationship with children) Subscales from the Family Adaptability and Cohesion Evaluation Scale (FACES III: Olson *et al.*, 1985).

Sample characteristics and descriptive data: Participants in the study were drawn from a cohort of 162 women admitted to a New Haven-based methadone program. Complete data was available for 125 women with at least one biological child. On average, mothers in the sample were 36 years old (SD = 6.1), had 2.7 biological children (SD = 1.3), completed high school (SD = 1.9), and had used opiates for 13 years (SD = 12.7). The majority of the mothers were single (85.4%), minority (41% African American, 16% Hispanic), and unemployed (67.5%). Descriptive data are presented in Table 1. Mean scores fell beyond clinical cut-off scores on all indices except peer support and perceived family adaptability.

Table 1. Descriptive data for all measures

	Mean	SD	% Beyond[a]
BDI	9.2*	7.2	50.0
ASI: Drug Use Severity	.20[n/a]	.10	n/a
PBI: Care	21.7*	7.9	38.4
PBI: Overprotection	17.3*	6.6	30.0
PSSS: Family	13.2*	5.0	33.6
PSSS: Peer	13.3	6.0	24.0
FACES: Adaptability	30.5	9.0	20.0
FACES: Cohesion	26.9*	6.4	94.0

[a] % beyond clinical cut-off score which was defined as 2 SD's beyond means reported for normative samples.

Data analyses and results: To examine how risk factors worked together, we used a "building block" strategy outlined by Kraemer & colleagues (2001), examining associations among co-occurring factors first (current support, depression, and drug use severity), and temporal (mediating) relations second.

Analysis of co-occurring factors: Correlations between co-occurring factors (perceived support, depression, and drug use severity) and family adaptability ranged from .26 ($p<.05$) to .45 ($p<.01$). Correlations between co-occurring factors and family cohesion ranged from -.08 (ns) to .16 (ns). We regressed family adaptability on 3 possible combinations of predictor pairs. When paired with perceived support, depression accounted for 00% unique variance, perceived support accounted for 13% unique variance, and 9% variance was shared. When paired with perceived support, drug use severity accounted for 2% unique variance, perceived support accounted for 16% variance, and 4% variance was shared. When paired with depression, drug use severity accounted for 4% unique variance, drug use explained 4% unique variance, and 4% variance was shared. We then regressed family adaptability on all 3 co-occurring variables simultaneously. Perceived support explained 7% unique variance, depression explained no unique variance, drug use severity explained 1% unique variance, and 15% variance was shared. Together, these findings suggest that depression and drug use severity meet criteria as *proxies* for, or *symptoms* of the more global disturbance – absence of perceived support.

Analyses of temporal (mediating) relations among factors: To test current perceived support as mediator of association between perceptions of early bonding experience and perceptions of parenting problems, we followed guidelines suggested by Baron & Kenny (1986). Early bonding experience predicted significant variance in perceived support, $R^2 = .23$, $p < .001$, and in one parenting outcome (family adaptability, $R^2 = .12$, $p < .05$). Perceived support predicted significant variance in one parenting outcome (family adaptability, $R^2 = .21$, $p < .001$).

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After perceived support was entered as a covariate, the association between early bonding experience and family adaptability was reduced by 83% ($R^2 = .02$, ns). The second outcome, family cohesion, was associated with few variables and did not meet criteria for mediation analyses.

Conclusions and implications: This study provides preliminary evidence that (a) the impact of depression and drug use severity on parenting relationships of drug-dependent women with their children may be a function of a more global disturbance in perceptions of support and nurture available in mothers' everyday lives; and (b) rather than having a direct influence on parenting, early bonding experience may influence how mothers perceive the availability of social support in their everyday lives, which, in turn, may influence the problems they experience relating to their children. This study also revealed poor family cohesion in 94% of mothers sampled; this restricted range may have precluded identification of meaningful associations with other factors. It will be important for future research to examine mechanisms underlying psychosocial risks for maternal addiction and maladaptive parenting, with particular attention to the absence of perceived support and nurture in everyday life and the absence of family cohesion.

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BEING AN ADDICT AND BEING A MOTHER: ROLE STRAIN AND ITS IMPACT ON PARENTING FROM THE PERSPECTIVE OF ADDICTED MOTHERS AND THEIR DAUGHTERS

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The main objectives of this paper are (1) to use family theory to explore the relationship between drug using mothers and their adult daughters; and (2) to present the mother-daughter relationship from the phenomenological perspective of both women.

As part of a larger cross-sectional community-based study among 250 women, data were collected using individual in-depth life history interviews, questionnaire-based interviews, focus groups, and, among one-third of the sample, observations of home environments and mother-daughter interactions. Sampling involved ethnographic mapping and targeted, chain referral and theoretical sampling. Eligibility criteria included being 18 or older, a member of a mother-daughter dyad in which both agreed to enroll, residing in Atlanta, not being in an institutional setting, having no cognitive impairments, and, for drug users, having used illicit drugs at least once during the last six months. This paper focuses on a sub-sample of 30 dyads in which all mothers used drugs. Among the daughters one-half used drugs (n=15), while the other one-half did not (n=15).

The mean age of the mothers was 44 years, the mean age of the using daughters was 25 years, and the non-using daughters 22 years. The daughters' level of educational attainment was significantly (p< .05) higher than among the mothers with 58.9% of the non-using daughters, 55.8% of the using daughters, and 41.7% of the mothers having at least a high school diploma or GED. Employment for at least 30 hours per week was significantly (p< .01) higher among the non-using daughters (25%) as compared to the using daughters (4.4%) and the mothers (2.0%). Almost all daughters had minor children, including 98.6% of the non-using and 93.3% of the using daughters. Among the mothers, 12.5% reported minor children. Using daughters were significantly (p< .05) more likely to know of their mothers' drug use than the non-using daughters (91.7% versus 77.8%). Among the mothers of using daughters, 75% knew of their offspring's use.

In women's lives, their affective bond with their mother is one of the most fundamental relationships, although also one of the more complex ties (Chodorow, 1978; Gilligan, 1982). The mother-daughter dyad is characterized by ambiguity and two key dimensions of the relationship are conflict and cohesion (Rossi and Rossi, 1990). In those mother-daughter relationships in which the mother is a substance user, additional complexities are present (Sterk, 1999). For example, maternal addiction is likely to result in parenting difficulties in areas such as enforcing discipline, monitoring, and problem solving. Ineffective parenting practices are likely to result in role strain for the mothers.

The mother-daughter relationship only can be understood when placed in the larger context of the household. When exploring household characteristics, it appeared that the non-using daughters were more likely to be the oldest child than the using daughters. No other differences were identified by the presence of other siblings in the household when the daughters were growing up. A substantial number of the using mothers resided with their non-using daughters. It was not uncommon for the daughters to experience role reversal and to function as the main caretaker and adult in the relationship. Women in those dyads in which both used drugs tended not to reside together; if they did, it often was in the home of the mother's mother or another female relative. Conflict was most common in households in which multiple substance abusers resided.

In addition, drug-using women's reproductive lives frequently are characterized by unplanned pregnancies and motherhood at a young age. Early motherhood results in an age-condensed family structure (Kaplan, 1996; Burton *et al.*, 1994). The generations are even more blurred if the daughter had an early pregnancy as well, which is more likely among those daughters who are substance users. The generational distance between the using and non-using daughters and their mothers was did not differ significantly and the mean generational age difference was 15.5 years. Age-condensed mother-daughter relationships present challenges that are inconsistent with their traditional generational position. For example, an adolescent daughter who becomes a mother faces tension between the adult-status due to her motherhood, while legally and developmentally still being an adolescent. The mother also faces an accelerated life course as she prematurely shifts to grandmotherhood. The close generational distance between mothers and daughters led the relationship to shift in the direction of siblinghood.

When exploring solidarity and closeness among the mothers and daughters, non-using daughters reported higher levels of associational solidarity than the using daughters. They interacted more frequently with their mothers and when they shared in activities both women referred to the time together as being of a high quality. Using daughters, on the other hand, reported higher levels of affectional solidarity or closeness. Independent of their drug use status, the daughters indicated lower levels of consensual solidarity (shared values, norms and beliefs) than the mothers.

Lessons learned so far include that maternal drug use clearly impacts the mother-daughter relationship and that family theories combined with a phenomenological perspective allow for an in-depth investigation. Many women referred to their relationship as "intimate but distant." It also is important to acknowledge that not all daughters of using mothers become drug users themselves. The relationship between mothers and daughters does not occur in a vacuum and needs to be explored within the context of the household; for instance, by considering birth order and family composition. Mother-daughter dyads in which the mother uses drugs are likely to result in a condensed family structure, resulting in chronological and developmental challenges. While non-using daughters report more associational solidarity, using daughters indicate more affectional solidarity. Overall, the mothers had a more positive perception of the closeness with their daughters than their offspring. Those mothers with the most positive view also reported more guilt, shame and role strain.

Further research in the mother-daughter relationship and the impact of maternal substance use is required. The current study had a number of limitations such as its cross-sectional design, the high reliance on self-reported information, the sample limitations of only including mothers and daughters, and the relatively small sample size. Some of the study's strengths include the in-depth data collection from both mothers and daughters in the same dyad, the community-based nature of the study, and the inclusion of the quantitative and the qualitative research paradigm.

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REFLECTIVE FUNCTIONING AS MEDIATOR BETWEEN DRUG USE, PARENTING STRESS AND CHILD BEHAVIOR

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Reflective Functioning (RF) has been proposed as a measure of a parent's internal representation of her relationship with her child (Fonagy, 1996; Slade *et al.*, 2000), and has been shown to mediate the relation between the quality of a mother's attachment to her own mother, and attachment quality with her child (Slade *et al.*, 2001). Reflective Functioning as a construct appears to describe aspects of the affective and relational representations that parents employ, and as a result, may mediate the quality of mother-child dyadic interactions, including mothers' perceptions of parenting stress and ratings of their child's behavior.

Methods: Women were recruited from an ongoing longitudinal evaluation of the developmental effects of prenatal cocaine exposure. In the longitudinal study women were recruited either immediately pre or post-natally at Yale New Haven Hospital. When women were recruited they were administered the Addiction Severity Index (ASI: McLellan et al., 1992) and their urine was tested for evidence of drug use. Either self-report of use during pregnancy or positive urine toxicology dictated assignment to one of two drug-exposed groups (drug-use-with cocaine, drug-use-without cocaine). If self-report and urine toxicology were negative for drug use, women were assigned to the non-drug-using group.

Recruitment to present study: Women with children over the age of 4 years old and who had custody of their children were asked to participate. A total of 58 women were eligible (18 non-drug-users, 10 drug-without-cocaine, 30 drug-with-cocaine) and participated in the study.

Procedure: Women were interviewed during a semi-annual visit to the lab where their children are regularly evaluated as part of the larger longitudinal study; participants were paid $20 for their participation. Women were administered the Parent Development Interview (PDI: Aber et al., 1985), which was transcribed and coded for RF using a manual developed by Slade and colleagues (Slade et al., 2000). During the course of semi-annual visits in the longitudinal study, women were also asked to complete the Parent report version of the Behavior Assessment Scale for Children (BASC: Reynolds and Kamphaus, 1992) at the 48 month visit and the Parenting Stress Index (PSI: Abidin) at the 54 month visit.

Results: A series of analyses were conducted to evaluate whether RF mediated the relation between Drug-Use status and the Social Skills subscale of the BASC, Parenting Distress and Parent - Child Dysfunctional Interaction subscales of the PSI. In each figure R^2 values are reported both with and without RF entered into the regression.

Figure 1: RF Mediating Social Skills Ratings

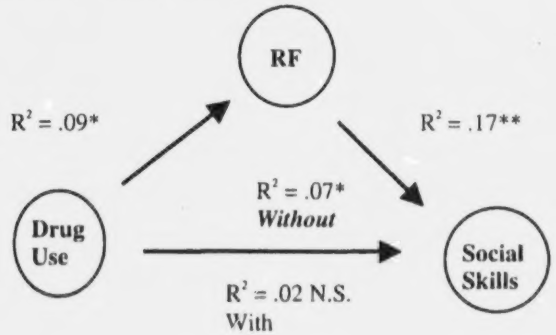


Figure 2: RF Mediating Parent Distress

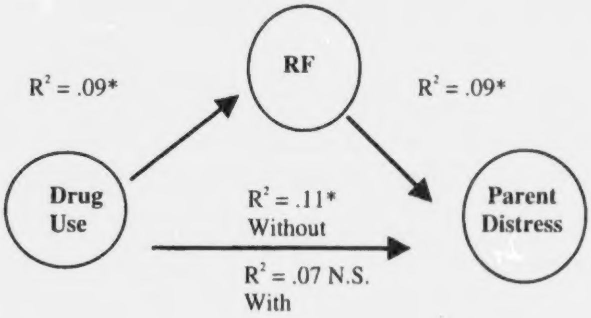
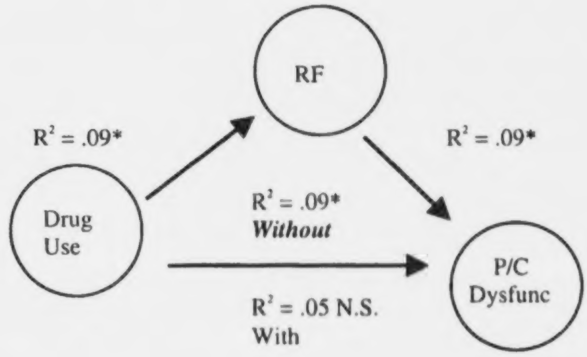


Figure 3: RF Mediating Parent – Child Dysfunctional Interaction



Discussion: Maternal RF mediated parent distress, parent-child dysfunctional interaction and social skills in their children. These findings suggest that a range of maternal variables, including mothers' internal representations of their relationships with their children, should be considered as potentially important contributors to developmental outcomes in high risk families.

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DRUG DEPENDENCE, REPRODUCTIVE STRATEGY, AND PSYCHOLOGICAL REPRESENTATIONS OF FATHERING

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Background: Over the course of the past 20 years, a number of social forces have converged in this culture to make fatherhood one of the more prominent public policy issues of the new millennium. Within policy statements identifying fatherhood as a social issue (e.g., see Federal Interagency Forum, 1998), researchers have repeatedly emphasized the need for more information concerning patterns of procreation among men, particularly disenfranchised populations of men assumed to be at risk for socially irresponsible production of children. Moreover, in their widely cited paper on the determinants of reproductive strategy, Belsky *et al.*, (1991) outlined a developmental process that highlights ways early experiences representing risk for chronic drug abuse also represent risk for pursuit of a personally adaptive, but socially irresponsible, reproductive strategy characterized by the early conception of multiple children in difficult social circumstances. However, although developmental theory suggests that drug-abusing men should be fathering children in a socially irresponsible manner, it is not clear to what extent this is true. Consequently, this study was designed to clarify (a) ways the reproductive strategy of drug-dependent fathers differs from that of men with no history of alcohol or drug abuse and (b) ways differences in psychological representations of fathering might account for differences in reproductive strategy otherwise attributable to drug dependence.

Method: Two ethnically diverse groups of largely middle-aged fathers were enrolled in this study. One hundred and ten (110) opioid-dependent fathers who were enrolled in methadone maintenance treatment were recruited via referral from drug counselors, announcements in waiting areas, and a simple system of peer referral. One hundred and nineteen (119) demographically matched fathers who were living in the same community with no history of drug or alcohol abuse since the birth of their oldest child were also recruited via announcements posted in public places and the same system of peer referral.

All subjects admitted to the study completed a structured interview and battery of self-report instruments designed to characterize their psychosocial adjustment as parents. In this preliminary study, drug dependence was represented categorically, data collected with the structured interview were used to define nine dimensions of reproductive strategy, and two self-report instruments were used to measure psychological representations of fathering. The Parental Acceptance Rejection Questionnaire (PARQ: Rohner, 1991) was used to measure quality of early relationships with biological fathers, and the Inventory of Father Involvement (IFI: Hawkins *et al.*, 2002) was used to measure personal definitions of the fathering role.

A series of linear regression analyses was then done to determine the extent to which psychological representations of fathering mediate differences in reproductive strategy associated with drug dependence. In all analyses, age and ethnicity were entered as covariates. In the series of analyses testing for mediation effects, both linear and quadratic representations of early relationships with biological fathers were included in the statistical model to allow for the fact that other research suggests men with very positive and very negative relationships with their fathers may make the greatest effort to be a responsible parent across generations.

Results: In a series of linear regression analyses comparing the reproductive strategy being pursued by the drug-dependent fathers with that of fathers living in the same community with no history of drug or alcohol abuse since the birth of their oldest child, the drug-dependent fathers were clearly pursuing a shorter-term, socially irresponsible reproductive strategy. With the Type I error rate held constant at .01 per analysis, there were statistically significant differences in all nine dimensions of reproductive strategy after allowance for age and ethnicity. Least-square means indicated that (a) the drug-dependent men began having children at an earlier age, (b) they had fathered more biological children, (d) they had been involved in fewer legal marriages, (e) they had lived with more women as sexual partners, (c) they had fathered children with more women, (e) their children were less likely to have been given their surname, (f) their children were less likely to have them listed on their birth certificate, (g) they had less education, and (h) they had less earning potential.

In a second series of linear regression analyses, the drug-dependent fathers also presented with differences in psychological representations of fathering. Again, with the Type I error rate held constant at .01 per analysis, there were significant differences in both current and historical representations of fathering after allowance for age and ethnicity. Least-square means indicated that (a) the drug-dependent fathers confirmed both perception of greater disturbance in their early relationship with their biological fathers and (b) they reported narrower personal definitions of the fathering role for themselves.

In a final series of linear regression analyses, there was evidence of partial mediation of differences in reproductive strategy by the differences in psychological representations of fathering. Again, with the Type I error rate held constant at .01 per analysis, there were significant curvilinear relationships involving quality of early father-child relationships indicating that relatively positive and relatively negative perceptions of early relationships with biological fathers were associated with (a) having children with fewer women, (b) being involved in more legal marriages, and (c) having more education. There were also significant relationships between personal definitions of the fathering role and specific dimensions of reproductive strategy indicating that a broader, more progressive definition was associated with (a) fewer coparenting relationships, (b) fewer cohabitations, (c) greater likelihood children had their father's surname, and (d) greater likelihood children had their father's name listed on their birth certificate. In a statistical model that included age, ethnicity, and drug dependence, psychological representations of fathering accounted for between 10 and 60 percent of the variance originally attributed to drug dependence.

Conclusions: Taken together, these preliminary results support some initial conclusions about psychological representations of fathering, drug dependence, and reproductive strategy. First, the results suggest that drug-dependence is associated with pursuit of a shorter-term reproductive strategy characterized by an earlier onset of parenthood and production of more children with more women in the context of (a) less stable sexual partnerships, (b) less social capital, and (c) less commitment to parenting. Second, the results suggest that drug dependence is also associated with perception of poorer early relationships with biological fathers and narrower personal definitions of the fathering role. Third, the results suggest that psychological representations of fathering may contribute to differences in reproductive strategy primarily through their influence on (a) educational achievement, (b) the nature of relationships with sexual partners, and (c) acknowledgment of paternity. Finally, there was some evidence that, independent of drug dependence, psychological representations of poor early relationships with biological fathers may invoke compensatory mechanisms in some men that contribute to pursuit of a socially responsible reproductive strategy. If replicated with larger, more representative samples of drug-dependent fathers, the results have implications for the development of preventive interventions designed to promote more responsible fathering among drug-abusing men.

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DISCUSSANT'S REMARKS

K. Kaltenbach

Thomas Jefferson University, Philadelphia, PA

The research presented in this symposium is most interesting and offers great promise to providing a better understanding of the parenting dynamics of drug dependent mothers and fathers. However, more significantly, this research represents the emergence of a "third generation" of research addressing these important questions.

Since the mid 1970's we've been investigating the effects of parental substance abuse and the outcome of the child. During that time we've moved from the first generation research to second generation research and to the presentations in this symposium that I would suggest, are the beginnings of a third generation of research.
In the first generation of research throughout the 70's and 80's studies were characterized by a bi-variate approach with relatively no attention given to multiple confounding factors. We all know the limitations associated with that work. Since the late 1980's we have experienced an appreciation that when investigating the effects of prenatal drug exposure, not only biological factors but also psychological, social, and environmental factors must be taken into account. However, this second generation of research has focused primarily on identifying and controlling these numerous confounding factors and we are still left with many unanswered questions.

Within this historical context we can trace a developmental evolution in terms of research methodology. However, it has yet to fully evolve into a paradigm shift – a paradigm that reflects the need to fully understand the psychosocial variables associated with parental substance abuse and how they effect the developmental outcome of the child. The research presented in this symposium represents efforts to make that shift.

As early as 1984, in a review of existing studies of developmental outcome of children exposed to methadone, the need to examine maternal personality traits, degrees of life stress, patterns of child care and qualitative characteristics of mother-child interaction was identified. While we have made significant strides in delineating the psychosocial characteristics of substance abusing women, and their association with maladaptive parenting, the work presented here takes us to the next step, which is an attempt to understand mechanisms of influence underlying these associations.

Too often when we investigate effects of maternal drug dependence on their children, we tend to focus on the drug use to the extent that we neglect to frame our research within a theoretical developmental perspective. However, a theoretical developmental perspective is essential if we are to understand the mechanisms that affect developmental outcome. It is only through such an approach that we can delineate the underlying processes that impact on the behavior of drug dependent parents and the outcome of their children.

Although the work presented in this symposium must be considered preliminary, hopefully it is representative of a new direction that will serve as the foundation for the third generation of research. Research that will enable us to better understand potential mediators of both risk and protective factors associated with child outcomes in families affected with parental addiction.

SYMPOSIUM IV

DRUG REWARD IN HUMANS: WHAT DOES DOPAMINE DO?

Harriet de Wit, Chairperson

DOPAMINE ANTAGONISTS AND RESPONSES TO STIMULANT DRUGS IN HUMANS

H. de Wit, M. Haney, T.R. Kosten, S.L. Walsh and M.J. Kuhar

Introduction: This symposium reviewed current knowledge about the role of dopamine in the rewarding effects of abused drugs. Dopamine is clearly implicated in the reinforcing effects of stimulant drugs in laboratory animals. Studies of drug self-administration and place preference in animals indicate that drugs which increase dopamine engender drug-seeking and preference, whereas drugs which block dopamine function interfere with positive, drug-motivated behaviors. The exact role of dopamine, however, has been the subject of controversy. The simplest hypothesis is that increases in dopamine produce feelings of well-being and euphoria. Indeed, most drugs that are self-administered by animals and abused by humans produce feelings of subjective well-being. Surprisingly, however, it has been very difficult to show that dopamine is involved in the mood-enhancing effects of stimulant drugs in humans. This symposium summarizes the findings from several lines of research showing that the role of dopamine in the reinforcing effects of drugs may be more complex. Dopamine receptor antagonists do not reliably dampen the acute, euphorigenic effects of stimulant drugs in human drug users or in healthy volunteers, suggesting that dopamine does not simply mediate drug-induced euphoria. Nevertheless, the possibility remains that the negative findings with dopamine and euphoria in humans are related to methodological differences between human and non-human studies.

DOPAMINE ANTAGONISTS AND RESPONSES TO STIMULANT DRUGS IN HEALTHY VOLUNTEERS

H. de Wit

Our laboratory has conducted a series of studies investigating the effects of dopamine antagonists on the acute, mood-enhancing effects of stimulant drugs in healthy volunteers. Healthy volunteers provide an excellent model for assessing the euphorigenic effects of stimulant drugs, because these subjects lack the expectancies and pharmacological adaptations typical of individuals with extensive drugs use histories. The subjective, or mood-altering effects of stimulant drugs can be quantified using standardized self-report questionnaires, and expectancies can be reduced by administering the drugs under double-blind conditions. In an early series of studies (Brauer and de Wit 1995; 1996; 1997; Brauer *et al.*, 1997) we investigated the effects of the dopamine antagonists pimozide (up to 8 mg) and fluphenazine on the mood-altering effects of d-amphetamine (5-20 mg). We tested increasing doses of pimozide across studies, up to a dose that produced sedative-like subjective effects of its own. Amphetamine reliably increased subjective reports of feelings of well-being, energy and euphoria. However, contrary to our expectations, neither of the dopamine antagonists attenuated any of the mood-enhancing effects of d-amphetamine.

Recently, we (Wachtel *et al.*, in press) have tested the effects of the dopamine antagonist haloperidol (3 mg), and the mixed dopamine-serotonin antagonist risperidone (0.75 mg), on responses to an acute dose of methamphetamine (20 mg) in healthy volunteers (N=17, 18). Risperidone was tested to explore the possibility that the euphoriant effects of stimulants may result from the combined effects of both dopamine and serotonin systems. As in the previous studies, however, neither of these antagonists attenuated any of the subjective or behavioral effects of methamphetamine, even though the doses of both drugs were high enough to produce some effects of their own (risperidone increased ratings of "feel drug" and haloperidol impaired performance on a psychomotor task). These findings further extend the findings that acute administration of dopamine receptor antagonists fail to attenuate the euphoriant effects of stimulant drugs in healthy volunteers.

These findings raise important questions about the role of dopamine in the reinforcing effects of drugs in animals. Although euphoria cannot be measured in non-verbal animals, it is often assumed that subjective drug effects play an important role in drug-seeking in animals as well as humans. It has sometimes also been assumed that reinforcing effects of drugs are related to their subjective effects. The present results raise questions about these assumptions. Future studies should explore other ways in which dopamine might mediate drug-seeking behavior in humans, including by mediation of conditioned effects or incentive-motivational effects.

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DOPAMINE ANTAGONISTS AND RESPONSE TO COCAINE IN COCAINE USERS

M. Haney

There is currently no effective pharmacotherapy available to treat cocaine dependence. The reinforcing effects of cocaine reinforcing appear to be mediated by inhibition of dopamine re-uptake, resulting in dose-dependent increases in extracellular dopamine levels in several brain regions. Thus, one potential approach for treating cocaine abuse is to pharmacologically block the dopamine receptor.

Five dopamine receptor subtypes have been identified, and these are subdivided into two families of receptors, the D1 (D1/D5) and D2 (D2/D3/D4) family. Although both of these receptor families contribute to the reinforcing and discriminative stimulus effects of cocaine, D2 antagonists are associated with extrapyramidal side effects that limit their clinical utility for cocaine abuse. By contrast, D1 antagonists do not produce extrapyramidal side-effects. D1 antagonists block cocaine's discriminative stimulus effects in rats and monkeys and also protect against the cardiovascular toxicity and lethality of cocaine in laboratory animals. In humans, it was recently reported that a single dose of the D1 antagonist, ecopipam dose-dependently decreased the effects of intravenous cocaine on ratings of "High" and "Good drug effect" and decreased desire for cocaine (Romach *et al.*, 1999).

The present study extended the Romach *et al.*, (1999) study by administering ecopipam repeatedly for several days, and by measuring self-administration of smoked cocaine. Cocaine users residing on an inpatient research unit received daily doses of placebo or ecopipam in a cross-over design. They were given the opportunity to self-administer cocaine (or engage in alternative behaviors) over several hours, under careful medical observation. The effects of ecopipam on cocaine self-administration, cocaine "craving," subjective-effects ratings, and cardiovascular effects were determined.

The participants (n=10) in the study spent an average of $251 per week on cocaine, and none were interested in treatment for their cocaine use. Subjects received active or placebo ecopipam for 5 days before 8 cocaine choice sessions. On the choice sessions, subjects were tested with four doses of smoked cocaine (0, 12, 25, 50 mg) during

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6 trials. On the first "trial" subjects sampled the cocaine dose available that day, and on the next 5 trials they were give a choice between smoking the available cocaine dose or receiving a $5 merchandise vouchers.

During placebo maintenance, subjects dose-dependently chose to take the cocaine over the merchandise, and cocaine dose-dependently increased subjective effects, craving for cocaine and nicotine, and cardiovascular parameters. During ecopipam maintenance, subjects chose significantly more of the low dose of cocaine (12 mg). Ecopipam increased ratings of cocaine dose quality, and how much participants would pay for cocaine (25, 50 mg), and it increased ratings of "Good drug effect," and "High" (50 mg). Ecopipam significantly decreased cocaine craving, yet doubled ratings of nicotine craving. Ecopipam also produced small but significant increases in heart rate and blood pressure in combination with cocaine (Haney *et al.*, 2001).

Thus, maintenance on the long-acting dopamine D1 antagonist, ecopipam, increased, rather than decreased, both cocaine self-administration as well as its subjective effects compared to maintenance on placebo. By contrast, ecopipam significantly decreased cocaine craving. A dissociation between craving for cocaine and its self administration is not uncommon, and emphasizes the importance of measuring self-administration when investigating potential pharmacotherapies. Although a medication that decreases cocaine craving under placebo cocaine conditions could theoretically decrease the likelihood of relapse in a treatment seeker, the fact that all of cocaine's effects would be enhanced if a relapse occurred does not suggest ecopipam would be an effective medication to treat cocaine abuse.

It is likely that the chronic, vs acute, administration of ecopipam was key to the outcome in the present study. Although acute pretreatment with D1 antagonists in rats, humans and monkeys blocked cocaine's stimulatory and discriminative stimulus effects, chronic administration of dopamine antagonists often results in a diminution or reversal of the effects seen following acute administration. For example, in rats, acute dopamine D1 or D2 antagonist administration blocked cocaine's reinforcing, locomotor and discriminative stimulus effects, while chronic antagonist administration enhanced sensitivity to cocaine (Emmett-Oglesby and Mathis 1988; Kosten 1996). These behavioral shifts following chronic antagonist administration were associated with an increased density and sensitivity of D1 receptors (Creese and Chen 1985; White *et al.*, 1998). Termination of antagonist maintenance in monkeys resulted in increased responding for cocaine compared to the period prior to antagonist exposure (Kleven and Woolverton 1990). Overall, the data suggest that maintenance on a D1 antagonist results in dopamine receptor supersensitivity, which increases the reinforcing and subjective effects of cocaine. Both the laboratory animal data and the present findings support the suggestion by Kosten (1997) that therapeutic maintenance on neuroleptics may contribute to the high incidence of cocaine abuse seen in schizophrenics.

To conclude, maintenance on the dopamine D1 antagonist, ecopipam, increased self-administration of a low cocaine dose, while enhancing the subjective effects of higher doses of cocaine. These data do not support the clinical efficacy of ecopipam for the treatment of cocaine dependence. Chronic administration of dopamine antagonists may produce adaptations that decrease their viability for the long-term treatment of cocaine abuse. Given the difference between the acute effects of ecopipam as compared to its chronic effects, animal models of medication development for cocaine abuse that administer drugs chronically may be most useful prior to human application.

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A NOVEL DOPAMINE AGONIST APPROACH TO TREATING COCAINE DEPENDENCE WITH DISULFIRAM

T.R. Kosten

Dopamine agonists have been tested as treatments for alcohol and stimulant dependence, because dopamine is thought to be a final common pathway of reinforcement and because chronic use of these substances results in low levels of dopamine (Bowers *et al.*, 1998). Randomized clinical trials have been conducted with the direct dopamine D2 agonists bromocriptine and pergolide, as well as indirect agonists that decrease dopamine breakdown, increase dopamine release or prevent inactivation of dopamine by blocking re-uptake back into the neuron that released it (e.g., mazindol, stimulants, selegiline and possibly disulfiram). Antagonists of dopamine have shown limited promise in clinical studies.

Although early studies used bromocriptine to relieve alcohol withdrawal symptoms, subsequent controlled studies failed to replicate these findings and showed no difference in alcohol use in 6 month trials (Kosten *et al.* ,2002 for references). Powell *et al.*, (1995) compared nortriptyline and placebo to bromocriptine in 216 male alcoholics in a 6-month trial and failed to find any attenuation of drinking by bromocriptine. Naranjo *et al.*, (1997) conducted a randomized, double-blind, placebo-controlled international, multicenter study to assess the effects of a long-acting injectable preparation of bromocriptine, a dopamine agonist, (Parlodel-LAR) in reducing relapse in 366 moderately/severely dependent alcoholics (DSM-III-R). After detoxification, they were randomized to receive six monthly injections of bromocriptine 25 mg (n = 120), bromocriptine 50 mg (n = 124), placebo (n = 122). At 6 months, there were no significant differences between treatment groups in rates of relapse on several measures of alcohol consumption.

More recently another agent, pergolide, a mixed D(1)/D(2) dopamine receptor agonist, was examined in 358 combined alcohol and cocaine dependent patients. In this 12-week, double-blind, placebo-controlled clinical trial of two doses of pergolide (0.05 and 0.25 mg bid), pergolide had no significant effect on alcohol use in the comorbid alcohol/cocaine dependence group and did not appear to have clinical value in decreasing alcohol use at these doses (Malcolm *et al.*, 2000).

Several direct and indirect dopamine agonists have been tested as treatments for cocaine abuse, but the results have been mixed. In a recent large placebo-controlled outpatient study, pergolide did not reduce cocaine use and

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produced significant side effects among alcohol and cocaine dependent patients (Malcolm *et al.*,2000;). In another trial, methylphenidate and sustained release methamphetamine improved treatment retention, and did not increase (but also did not decrease) cocaine use (Grabowski *et al.*, 1997). The dopamine reuptake blocker mazindol was ineffective as a treatment for cocaine use (Stine *et al.*, 1995). In one double-blind, placebo-controlled trial of 42 patients over 10 days, amantadine showed some efficacy at the two week and one-month follow-up visits (Alterman *et al.*, 1992), and the monoamine oxidate type B inhibitor L-deprenyl (selegiline) (10 mg) attenuated some subjective effects of cocaine, and reduced cocaine use in an outpatient trial (Bartzokis *et al.*, 1999; Vocci, personal communication 2000). Thus the findings with dopamine agonists as treatments for cocaine abuse have been modest.

Disulfiram is an aldehyde dehydrogenase as well as dopamine beta hydoxylase (DBH) inhibitor used in treating alcoholism, a common coexisting problem among cocaine abusers. The DBH enzyme converts dopamine to norepinephrine, and its inhibition leads to the release of dopamine from neurons that ordinarily release norepinephrine. Thus, overall dopamine release is increased yielding some dopamine agonist-like effects of this medication. One recent study in six cocaine dependent volunteers examined the effect of disulfiram 250 mg on responses to intranasal cocaine (2 mg/kg) using a randomized double-blind, placebo-controlled, design (McCance *et al.*, 1998). While disulfiram did not alter cocaine "high," it decreased craving for cocaine. Plasma cocaine concentrations were significantly higher while on disulfiram, which may have contributed to the decreased craving and increased dysphoria observed in some subjects. In a treatment study with patients who abused both alcohol and cocaine, Carroll *et al.*, (1998) found that disulfiram significantly reduced cocaine use compared to patients receiving psychotherapy alone,. The patients treated with disulfiram reported a significantly lower percentage of cocaine use days, fewer days of cocaine use, and fewer positive urine screens for cocaine were observed. Three other placebo controlled studies also found disulfiram reduced cocaine abuse (George *et al.*, 2000, Carroll, personal communication 2002; Petrakis, personal communication 2002). These studies involved 20 to 115 patients and the overall percentage of cocaine free urines was 55% on disulfiram and 40% on the comparison, a significant difference across these 12 week trials.

In summary, direct dopamine agonists have failed for alcohol and stimulants, but indirect agents (selegiline and disulfiram) hold some promise for treatment of cocaine dependence.

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ROLE OF DOPAMINE AND KAPPA RECEPTORS IN SUBJECTIVE RESPONSE TO COCAINE

S.L. Walsh

There is a substantial body of data supporting a critical role for dopamine in the mediation of reward in general and, more specifically, in the mediation of the rewarding effects of drugs of abuse, including cocaine. Although cocaine exerts many pharmacological actions in the CNS and periphery, there has been a confluence of evidence suggesting that the rewarding effects of cocaine are mediated, in large part, through the mesolimbic dopamine system. Due to this prevailing theory, much of the research aimed at the identification and development of pharmacotherapies for cocaine dependence has focused on evaluating agents that modify dopamine neurotransmission.

This presentation described three completed studies that evaluated the impact of dopamine antagonism on the response to cocaine in humans. Three different strategies were employed to achieve dopamine blockade: 1) non-selective dopamine receptor blockade with the non-selective antagonist- alpha flupenthixol, 2) selective D1/D5-like receptor blockade with the D1/D5 antagonist, SCH 39166, and 3) indirect dopamine antagonism through a secondary neurochemical system – the kappa opiate system by employing enadoline, a selective kappa agonist and butorphanol, a putative mixed kappa and mu partial agonist.

Flupenthixol is used for its antipsychotic and antidepressant properties in Europe but not licensed in the United States. This study was conducted at two sites (Johns Hopkins and Columbia University) and employed a between-subjects, parallel-group design in which subjects were randomly assigned to receive one of three treatments-placebo, a low dose flupenthixol regimen or a high dose flupenthixol regimen (Evans *et al.*, 2001). Active dosing with flupenthixol was initiated with daily oral treatment (0, 2.5 or 5.0 mg) for 1 week and followed by a matched dose of a long-acting (2-week) intramuscular decanoate formulation (0, 10 or 20 mg, respectively). Dosing was double-blind. Subjects participated in the study for approximately 25 days in three sequential phases: a baseline period, a 1-week period of oral treatment and a 2-week period after the intramuscular treatment. During each period, subjects participated in an array of cocaine test sessions that could include cocaine safety sessions, fixed dose, dose response and self-administration sessions. During the cocaine fixed dose challenge sessions, cocaine (48 mg/70 kg, i.v.) was administered intravenously for four consecutive infusions at 14-min intervals beginning 4 hr after oral pretreatment.

Across a wide array of subjective measures, flupenthixol failed to significantly alter the effects of cocaine. These measures included visual analog ratings of "liking for cocaine," "good effects," and magnitude of "drug effect." Flupenthixol also failed to alter cocaine self-administration at either a low or high dose of cocaine. Moreover, although no significant physiological interactions between flupenthixol and cocaine were observed, the high dose regimen of flupenthixol alone produced extrapyramidal side effects (primarily oral dyskinesias) in two volunteers, requiring study discharge for those volunteers and cessation of enrollment into the high dose group. In sum, data from this study indicated that flupenthixol did not significantly alter the subjective effects of cocaine related to its abuse liability or suppress cocaine self-administration, and flupenthixol had an unacceptable side effect profile in this healthy population.

The second study evaluated the effects of SCH39166, also known as ecopipam, for its effects on the response to cocaine (Nann-Vernotica *et al.*, 2001). Ecopipam has been characterized as a selective antagonist for D1/D5-like receptors and is not currently marketed for any clinical indication. This study employed a within-subject crossover design (n=10). Subjects were maintained on each of four doses of ecopipam (0, 10, 50 and 100 mg, p.o.) for a 1-

week period; these 1-week blocks occurred in completely randomized order and all doses were administered under double-blind conditions. Four cocaine sessions conducted at the end of each study week were scheduled so that the cocaine challenge occurred after 6 days of dosing. Cocaine (0, 25 and 50 mg, i.v. at 1-hr intervals) was administered 20 hr after oral dosing with ecopipam.

Cocaine produced dose- and time-dependent increases on an array of subjective measures, including magnitude of drug effect, "liking for cocaine," "good effects," street value estimates of the dose and craving for cocaine. Ecopipam failed to modify the effects of cocaine on any of these measures across all active dose conditions. Ecopipam was well tolerated in combination with cocaine and produced only modest physiological interactions; ecopipam tended to increase the pressor response to cocaine. Data from the psychomotor performance task, digit symbol substitution, revealed that the highest dose of ecopipam impaired performance, thus confirming psychoactive effects in this dose range. In sum, the data from this study did not support the pursuit of ecopipam as a potential pharmacotherapy for cocaine because, although ecopipam was tolerated safely in combination with cocaine under these dose conditions, ecopipam failed to significantly modify the subjective effects of cocaine.

The third study evaluated the effects of enadoline (CI-977), a selective kappa agonist, and butorphanol, a mixed mu and kappa partial agonist to test their efficacy against cocaine on both subjective measures and self-administration (Walsh *et al.*, 2001). Seven doses were evaluated under double-blind conditions in a quasi-randomized order. For safety purposes, the enadoline test conditions were presented in ascending order and imposed on an otherwise random dose procedure for the first three subjects only. Once the safety of enadoline and cocaine in combination was established, all subsequent subjects received the doses in completely randomized order. The seven intramuscular test conditions were: placebo, enadoline (20, 40 and 80 μg/70 kg) and butorphanol (1.5, 3 and 6 mg/70 kg). Each of these doses was examined over a 1-week period under three different experimental cocaine test procedures. During the first session of each week, subjects received cocaine (0, 20 and 40 mg, i.v. 1 hr apart) beginning 30 min after administration of the assigned i.m. dose. During self-administration sessions, subjects had the opportunity to choose between cocaine (40 mg, i.v.) and an alternative reinforcer (various dollar amounts) during six trials. In one condition, a sample dose was given before the choice trials and the alternative reinforcer value was initially low, and in the second condition no sample dose was given and the alternative reinforcer was initially high. Choice trials were initiated 30 min after treatment with the i.m. test dose.

Analysis of the subjective effect measures revealed that enadoline tended to decrease the positive subjective effects of cocaine and did so significantly for a number of measures, including ratings of magnitude of drug effect, "high," "good effects," and "liking for cocaine." Post-hoc analyses revealed significant attenuation by the highest enadoline dose (80 ug/70 kg). In contrast, butorphanol failed to alter any of the subjective responses to cocaine over the full range of test doses. The two choice self-administration procedures yielded different baseline rates of cocaine taking, whereby significantly lower rates occurred when subjects were tested in a state of abstinence with the higher alternative reinforcers presented first. Neither enadoline nor butorphanol significantly altered cocaine choice behavior in either of these procedures. In summary, cocaine was tolerated safely when given in combination with both enadoline and butorphanol. Only the highest dose of enadoline significantly reduced some subjective responses to cocaine, although this dose was itself dysphoric. Neither enadoline nor butorphanol significantly altered cocaine self-administration.

In summary, these studies do not necessarily refute a role for dopamine in the mediation of the rewarding effects of cocaine. However, the present results do suggest that antagonism of dopamine, whether by direct or indirect blockade, does not produce clinically meaningful alterations in the response to cocaine in humans. It is possible that the level of dopamine blockade needed to alter the effects of cocaine cannot be achieved safely in humans without encountering significant side effects. These negative findings, in combination with other negative studies that have evaluated dopaminergic agents as potential treatments for cocaine dependence, may support pursuit of agents acting on multiple neurotransmitter targets.

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DISCUSSION

M.J. Kuhar

There is abundant and strong evidence from animal studies that mesolimbic dopamine is involved in the action of psychostimulants (Kuhar *et al.*, 1991, Everitt and Wolf 2002). However, as described here, dopamine receptor blockers have not (with one exception; Romach *et al.*, 1999) been effective in reducing the effects of cocaine in humans. Therefore, is the dopamine hypothesis invalid in humans, or is it misunderstood, or are the tests not yet definitive?

It is recognized that human trials for treatment of substance abuse can have design problems (Good Preclinical Statistical Practices Working Party 2002). However, it seems unlikely that ***all*** of the negative studies, some of which are summarized above, are flawed. Thus, for the purposes of this argument it is assumed that the negative results regarding the role of dopamine in the euphorigenic and reinforcing effects of stimulant drugs in humans are valid, and that other issues must be examined. One issue that has not been addressed in these studies is that the receptor antagonists used in these studies do not completely block all the involved receptors.

There are five types of dopamine receptors, numbered from 1 to 5. D1 and D5 are considered similar in that they both increase cAMP, while D2, D3 and D4 are grouped because they decrease cAMP (Nestler *et al.*, 2001). When we test a drug that blocks D2 receptors, for example, we must be aware that it may not block D3 and D4 receptors and that effects on second messengers such as cAMP may not be blocked because the other receptors still function. The same argument could be applied to experiments that block only D1s but do not affect D5s. Indeed, dopamine receptor blocking drugs vary widely in their potency at different receptors; for example, haloperidol has an IC50 at D2 receptors of about 0.5 nM, but is at least ten-fold weaker at D3 and D4 receptors. Therefore, doses of haloperidol that block D2 receptors to a significant degree will not block other receptors (D3 and D4 with similar cellular effects) at the same dose. It may be necessary to block all the receptors of the same class or group to be sure that a complete test has been made. This argument makes an assumption that all the receptors in a group can produce the same physiologic effect and that not blocking all of them will permit the effect. Given the strong evidence for the dopamine hypothesis in animals, it seems that we must entertain this possibility.

An obvious question is why do the drugs block drug-taking in animals but have few or no effects in humans. One possible answer is that animal brains are different from human brains. That is, the differences in drug effects may be due to differences in brain structure and localization of receptors. Alternatively, the dopamine hypothesis may hold in humans, but a different approach to testing it may be needed with humans. For example, given the pharmacological agents available for use with humans, multiple agents may be needed at the same time to produce more complete blockade of dopaminergic neurotransmission in order to test the hypothesis properly. It is possible and likely that the agents used in past human experiments have provided incomplete receptor blockade.

Some new findings with monkeys suggest some additional complexities in studying human populations. Recent cocaine self-administration studies in monkeys showed that social vs single housing and dominance status of the animals altered the amount of drug self-administered. These PET studies examined the availability of D2 receptors in monkeys that were initially housed singly and then moved to group housing. When social dominance patterns were established, it was found that the availability of D2 receptors increased in the animals that became dominant, whereas the subordinate animals showed no change. Moreover, cocaine became a more potent reinforcer in subordinate animals than in dominant ones (Morgan *et al.*, 2002; Kuhar 2002). These dramatic results indicate that both the neurochemistry of dopamine systems and cocaine use can depend on social factors. If this is applicable to humans, then these differences could produce different dopaminergic physiologies and higher variability in human populations depending on the makeup of the groups studied.

While these realizations and findings may make studies more difficult, they also help provide rationales for better and improved study designs.

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SYMPOSIUM V

MEDICAL CONSEQUENCES OF PROBLEMS OF DRUG DEPENDENCE

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INTRODUCTION

After two decades of public health attention, HIV/AIDS continues to rank as one of the leading health concerns in the United States and other nations. Given the continuing increase of HIV/AIDS and other infectious diseases among drug-using populations, this symposium will present an update on the epidemiology of HIV/AIDS, TB, hepatitis B and C, STDs, and neurocognitive functioning as consequences of drug dependence. Specific aims of the symposium are to provide the CPDD community information on current advances in research relating to HIV/AIDS, hepatitis B and C and other co-occurring infectious diseases, as well as to identify areas for future research. NIDA-funded scientists will present findings from their ongoing research studies. Topics addressed are: "Drug Influences on Executive Functions of Young Injection Drug Users," "Tuberculosis Among Drug Users," and "The Spectrum of Infectious Diseases Among Drug Users."

DRUG INFLUENCES ON EXECUTIVE FUNCTIONS OF YOUNG INJECTION DRUG USERS

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Background

Injection drug use accounts for nearly half of the annual incident HIV infections in the U.S. through direct transmission due to needle sharing and indirect transmission due to heterosexual contact with injection drug users (IDUS) (CDC, 2001). Further, landmark studies of HIV suggest that younger IDUs are at much higher risk than older IDUs to contract HIV (Nelson *et al.*, 1995). Alarming rates of HIV infection transmitted through high risk injection practices and sex behaviors among adolescent and young adult IDUs explain a large part of the reason why AIDS is the leading cause of death among persons 25-44 years old in Baltimore City. To the extent that variation in HIV-risk behaviors among IDUs is associated with a lack of impulse control, poor planning and decision making, or a failure to learn from experience or accurately weigh short-term rewards against longer-term consequences, then executive dysfunctions are probably involved (Fuster, 1997; Lezak, 1995).

The present study seeks to add to the literature on HIV epidemiology designed to prevent the spread of HIV by integrating two lines of inquiry that were previously separate. One line of research central to the proposed study has helped to clarify the importance of individual behaviors, such as high risk injection practices and sex behaviors, that promote risk of HIV infection and subsequent AIDS. A separate line of research has focused more generally upon the nature of and individual differences in the expression of executive functions, such as working memory, response inhibition, planning, and decision-making. What is intended in this research project is to yoke these two lines of research together. That is, the research plan uses what has been established as a set of standardized longitudinal assessments of HIV-risk behaviors and HIV-serostatus. The research plan also specifies a separately established set of standardized assessments of executive functioning. What is new is the integration of these lines of research in a single research plan that seeks to estimate (1) the degree to which HIV-serostatus might depend upon levels of executive functioning, and (2) the degree to which the HIV-risk behaviors that promote HIV-seroconversion might depend upon levels of executive functioning.

Accordingly, the research project has been organized in relation to two linked studies. In the first study, the strength of association between HIV-serostatus and levels of executive functioning will be examined. This will be accomplished via a case-control study of IDUs with and without HIV who will be administered a baseline neuropsychological assessment. The seropositive IDU cohort under study is one in which HIV infection is in relatively early stages, well before AIDS-related dementia and AIDS-associated impairments in executive functioning become a source of potentially serious confounding.

In the second study, the seronegative cohort will be re-assessed on three subsequent occasions, roughly six months apart, primarily to assess variation in the levels and occurrence of HIV-risk behaviors, the levels of drug-taking frequency, and the levels of executive functioning. The seronegative cohort under study is one in which the HIV-risk behaviors are expected to be at relatively higher levels and to show variation over time. Further, because this is an IDU sample, the research plan also creates an opportunity to investigate possible interdependencies that link levels of drug-taking frequency and levels of executive functioning to subsequent levels and occurrence of HIV-risk behaviors.

This presentation summarizes the background and preliminary findings of this new study to evaluate relationships between executive dysfunction, drug use type and frequency, HIV-risk behavior, and HIV seroconversion among injection drug users. The primary focus of the presentation is on the evaluation of drug influences on executive dysfunction. Initial findings are reported based on baseline assessments that have been conducted to date.

METHOD

Participants

To date, I 1 8 IDU participants have completed the baseline assessment battery. Six (5. *1* %) of these participants tested positive for HIV and were not included in the present study analyses. The remaining 112 participants were between 18 and 40 years of age (M= *27.95; SD* = 5.27) with nearly equal proportions of female (53.6%) and male (46.4%) IDUS. The ethnic/racial composition of the sample was 54.5% white, 41.9% African American, 2.7% Hispanic, and 1% Native American. Highest level of education ranged from grade six to three years of postsecondary school *(M= 10.35; SD* = 1.77). Shipley IQ ranged from a standard score of 70 to *115 (M= 93.47; SD* = 12.95).

Instruments

The baseline assessment battery is comprised of an HIV Risk Behavior Interview and neuropsychological assessments of cognitive functions. Blood and urine samples are also collected to ascertain HIV, HBV, and HCV statuses and to verify self-report of recent drug use. The HIV Risk Behavior Interview was adapted from tools developed during landmark studies of HIV-risk behavior (e.g., Vlahov *et al.*, 1991). The interview provides extensive information on high risk drug use and sex behaviors, obtaining data on illicit drug use (injection and noninjection), sexual activity (male and female regular, anonymous, client partners and new partners) and clinical symptoms (related to HIV infection, drug use or STDS).

Neuropsychological assessments of cognitive function include the following tests: the WAIS-III Digit Span subtest to assess working memory, Stroop to assess response inhibition, Trails A and B to assess cognitive flexibility, Tower of London to assess planning, the Wisconsin Card Sorting Task to assess conceptual reasoning, the Test of Variables of Attention to assess impulse control and attention, and finger tapping to assess motor speed.

Procedure

Study participants were recruited by trained project staff from a variety of community-based sources in the Baltimore metropolitan area. Recruitment involved outreach to young adult clubs, street outreach, treatment programs, local emergency rooms, and health clinics in the Baltimore region. Study assessments were administered by clinicians who received extensive training and ongoing supervision on neuropsychological and HIV-risk behavior assessment. Participants received financial remuneration for the assessment. Urine samples were collected from participants to validate self-report of recent substance use. Urine was analyzed for the presence of psychoactive substances, including cannabinoids, cocaine, opiates, amphetamine, methamphetamine, MDMA, benzodiazepines, and barbiturates using gas chromatography-mass spectrometry methods. Blood samples were collected to ascertain HIV status using standard ELISA screening and confirmatory Western Blots. Referrals to drug treatment and HIV counseling were provided to all study participants following established protocols.

Data Analysis Plan

Initially, descriptive statistics were used to ascertain base rates of lifetime drug use and rates of recent injection behaviors among the sample. Next, two series of multiple regressions were conducted: one examining relationships between lifetime drug use and neurocognitive functions and the second series examining relationships between drug use in the past 24 hours and neurocognitive functions. Dependent variables for both series of regressions were the following seven neuropsychological test scores: Digits Forward, Digits Backward, Trails B-minus-A, Stroop interference, Tower of London total moves, Tower of London total correct, and Wisconsin perseverative errors.

In the first set of analyses, one regression each was run for each neuropsychological test score with lifetime use of injection speedball, injection heroin, injection cocaine, snorting cocaine, smoking crack, and smoking marijuana as independent predictor variables. In the second set of analyses, one regression each was run for the same neuropsychological test scores with injection speedball, injection heroin, injection cocaine, and marijuana use during the past 24 hours as independent predictor variables. Snorting cocaine and smoking crack were not entered in the second set of analyses because of low base rates of recent use. In addition, analyses were run with and without Shipley IQ, age, and gender as control variables.

RESULTS

Rates of Lifetime Drug Use

Rates of ever having used a range of drugs were examined by various routes of administration (i.e., injection, sniff/snorted, smoked, swallowed) to provide additional descriptive information about the sample. The following percentages of participants reported lifetime use of speedball injection (90.2%), snorting speedball (42.9%), heroin injection (95.5%), snorting heroin (I 8.8%), smoking heroin (14.3%), injecting cocaine (84.8%), snorting cocaine (73.2%), injecting crack cocaine (I 1.6%), smoking crack cocaine (77.7%), snorting methamphetamine (17.0%), smoking methamphetamine (5.4%), swallowing ecstasy (28.6%), swallowing LSD (40.2%), swallowing tranquilizers, barbiturates, or sedatives (45.5%), smoking marijuana (92%), smoking hashish (48.2%), snorting inhalants (28.6%), swallowing mushrooms (24. 1 %), and smoking PCP (38.4%).

Rates of Recent Injection Drug Use Behaviors

To provide further descriptive information about the sample, rates of risky injection practices during the past six months were also examined. During the six months immediately preceding the baseline assessment, 49. 1 % of participants reported daily injection, 17.9% reported injection drug use every-other-day, 14.3% reported weekly injection, and 18.8% reported at least monthly injection. About 3% of participants reported injecting drugs 10 or more times a day with 13.4% reporting injection drug use 5 -to-9 times a day, 5 7. 1 % reporting injection drug use 2-to-4 times a day, and 26.8% reporting injecting drugs once daily. Rates of other risky injection practices exhibited during the past 6 months included needle sharing (37.5%), attendance at a shooting gallery where drug users congregate (3 4.8%), and backloading (24. 1 %).

Relationship Between Lifetime Drug Use and Neurocognitive Functions

Relationships between the number of years drugs had been used and neuropsychological test performance were examined. A greater number of years of using each of the six drug types (i.e., injection speedball, injection heroin, injection cocaine, snorting cocaine, smoking crack, and smoking marijuana) was associated with lower levels of performance on digits backward, a test of working memory. A greater number of years of snorting cocaine was the only substance examined associated with a lower level of performance on an attention task (i.e., digits forward). Conversely, lifetime use of each drug examined, except lifetime snorting of cocaine, was associated with lower levels of performance on the Stroop, a test of response inhibition. A greater number of years of speedball injection, cocaine injection, snorting cocaine, and smoking marijuana were associated with lower levels of performance on a measure of cognitive flexibility (Trails B minus A). Longer lifetime use of speedball injection, cocaine injection, snorting cocaine, and smoking crack were associated with lower levels of performance on a measure of conceptual reasoning (i.e., Wisconsin perseverative errors). Notably, lifetime use of none of the drugs examined was associated with performance on tests of planning ability (i.e., Tower of London total moves and total correct).

Relationship Between Drug Use in the Past 24 Hours and Neurocognitive Functions

Relationships between the amount in dollars spent on drugs used in the 24 hours immediately preceding the baseline assessment session and neuropsychological test performance were also examined. Counter to anticipated relationships, greater amounts of speedball injection and cocaine injection were associated with better performance on digits forward while greater marijuana use was associated with worse performance on this task. Recent speedball injection was also associated with better performance on digits backward but worse performance on Trails B-minus-A. A greater amount of heroin injection was associated with improved performance on the Stroop with a greater amount of cocaine injection associated with worse performance on this test. Greater amounts of recent speedball injection, heroin injection, and smoking marijuana were all associated with lower levels of performance on measures of planning (i.e., Tower of London total moves and total correct) and conceptual reasoning (i.e., Wisconsin perseverative errors).

DISCUSSION

Consistent with a growing base of research documenting how chronic drug abuse may produce brain disease (Bolla *et al.*, 2000; London *et al.*, 2000), lifetime use of certain drugs was associated with lower levels of performance on neurocognitive tasks in the present study. For example, chronic heroin injection and chronic cocaine injection were associated with decrements in working memory and interference control. In addition, chronic cocaine injection was also associated with decrements in conceptual reasoning and cognitive flexibility. Notably, chronic use of the drugs examined did not exhibit a negative influence on tests of planning ability.

Recent drug use had more variable effects on neurocognitive functions in this sample. For example, greater amounts of both heroin and cocaine injection during the past 24 hours were negatively associated with performances on tests of higher-order executive functions (e.g., planning and conceptual reasoning), yet were positively associated with performances on tests of attention, working memory, and response inhibition. This apparent contradiction in results may be explained, in part, by the influence of drug withdrawal on cognition. That is, following injection drug use, the user may experience certain cognitive benefits in the form of increased functioning in their ability to maintain attention. However, higher-order cognitive functions, such as the ability to plan behavior, identify how patterns of risk behavior may result in adverse outcomes, and the ability to change one's approach to problem solving appear to compromise acute drug effects.

To the extent that acute and long-term drug effects on the central nervous system are indeed variable, with chronic drug use resulting in declines in cognitive functions, yet recent drug use resulting in a mixed pattern of decline on some functions yet improved performance on others, a heretofore unknown cognitive basis for maintaining injection drug use may be at play. Namely, repeated drug self-administration among IDU may operate as a negative reinforcer not only by removing the painful and well-known physical consequences of heroin withdrawal, but by also removing the cognitive consequences of withdrawal, which may involve total cognitive disorganization. Unfortunately, while repeated self-administration of injection drugs may help to maintain basic cognitive functions in the short-term, which help to accomplish basic daily living behaviors, chronic drug use erodes many of the higher-order cognitive functions necessary to plan, enact, and monitor complex behavioral sequences. The future and primary aim of the present study is to examine the degree to which declines in cognitive functioning resulting from chronic drug use result in greater levels of risk behavior which, in turn, predispose IDUs to contract HIV.

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TUBERCULOSIS AMONG DRUG USERS

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Drug users are at increased risk for tuberculosis (TB) infection and disease (Perlman *et al.*, 1995). Unlike blood-borne infections (eg., HIV, hepatitis C virus), skin and soft-tissue infections, or endocarditis, for which the risks are directly related to the act of non-sterile drug use, the increased risks of tuberculosis are related instead to a convergence of social and demographic TB risk factors. These include poverty, unemployment, homelessness, incarceration, foreign birth, and HIV co-infection (Perlman *et al.*, 1995).

Rates of TB infection among drug users significantly exceed those of non-drug using controls. These rates increase significantly with both age and with years of drug use, the latter likely related to increased time spent in settings in which TB is transmitted (Salomon *et al.*, 2000). Among injection drug users (IDUs) at a New York City syringe exchange program, tuberculin skin test rates were 5% among IDUs aged ≤ 35 with < 5 years of drug use, 13% among those aged > 35 with < 5 years of drug use, 17% among those aged ≤ 35 with > 5 years of drug use, and 21% among IDUs > 35 with > 5 years of drug use (Salomon *et al.*, 2000). This cumulative increased risk supports recommendations for serial TB screening in drug users.

Traditional methods of TB contact tracing, based on named contacts from home, work or school settings, have limitations relevant to drug users, and miss contacts not known to index cases by name. Newer approaches incorporating ethnographic interviews and social network analyses reveal unsuspected links between cases and sites of TB transmission (Klovdahl *et al.*, 2001). These sites are frequently places where substances are used, eg., bars, crack houses, shooting galleries, and homeless shelters.

Both drug use, and the knowledge and attitudes drug users have about TB may adversely impact adherence to TB services (Salomon *et al.*, 1999). While most know that tuberculosis is contagious but can be treated and prevented, they confuse TB infection and disease; many erroneously think HIV-related tuberculosis cannot be treated (Salomon *et al.*, 1999). IDUs self-reports of prior positive TB skin tests are highly accurate but despite prior testing, many drug users are unaware of their own TB status (Salomon *et al.*, 2000). Among IDUs at a New York City syringe exchange program, not knowing that HIV-related TB could be treated was independently associated with worse adherence to TB testing (OR = 0.5) (Salomon *et al.*, 1999).

However, educational interventions, while important and appropriate, may be limited in the impact they have on adherence to TB services. In a randomized study of adherence to TB skin testing among street-recruited IDUs, a theory based motivational education session did not improve adherence, while modest monetary incentives ($5 or $10) had a potent impact. Malotte and colleagues observed approximately 33% adherence among those assigned to no intervention or motivational education only, 85% adherence among those receiving a $5 incentive with or without education, and 92% adherence among those receiving a $10 incentive with or without motivational education (Malotte *et al.*, 1998).

Approaches demonstrated to significantly enhance drug users' adherence to TB services include co-locating TB screening and preventive therapy in drug treatment programs (eg., methadone maintenance programs). Methadone maintenance program-based TB screening and preventive therapy has been shown to improve adherence and treatment completion compared with off-site referral, and to be both cost-effective and potentially cost saving (Gourevitch *et al.*, 1998; Batki *et al.*, 2002).

Strategies to conduct TB screening among the majority of drug users not in drug treatment at any given time include street-based recruitment and syringe exchange-based services (Perlman *et al.*, 1997; Paone *et al.*, 1998; Malotte *et al.*, 1998). Syringe exchange-based TB services result in high rates of adherence to TB skin testing, good directly observed preventive therapy completion rates, and are also cost effective and cost saving (Perlman *et al.*, 1997; Perlman *et al.*,1999; Fitzgerald *et al.*, 1999; Perlman *et al.*, 2001; Riley *et al.*, 2002). At a syringe exchange program in New York City, we observed a 96% acceptance rate of TB screening and a 91% rate of adherence to returning for skin test interpretation with $15 worth of incentive contingent on adherence ($5 transportation and $10 cash). An 84% adherence rate was observed at a Baltimore SEP ($5 check as incentive) (Riley *et al.*, 2002), and in Vancouver the addition of a $5 (Canadian) incentive was found to increase the return rate from 43% to 78% (p = .001) (Fitzgerald *et al.*, 1999).

We examined the cost-effectiveness of TB screening and preventive therapy delivered to IDUs at a syringe exchange program (Perlman *et al.*, 2001). We modeled the costs of tuberculosis treatment that would be averted by tuberculosis preventive therapy using program costs, observed tuberculosis infection prevalence rates, and literature estimates of isoniazid effectiveness, INH hepatotoxicity, and TB treatment costs. For 1,000 patients offered screening, incorporating real observed program adherence rates, directly observed preventive therapy for drug users on site at a syringe exchange would avert $179,934 in TB treatment costs, for a net savings of $123,081 (Perlman *et al.*, 2001).

However, while adherence to skin testing was excellent, adherence to referral for free chest x-rays (CXRs) without an incentive was only 34%, reducing the pool of IDUs eligible for preventive therapy. Incomplete adherence to this step of TB screening limits the ability to exclude active TB and to identify appropriate candidates for preventive therapy. Cost-modeling demonstrated that if a $25 incentive per person increased CXR adherence to 50% or 100%, that the net cost savings of TB treatment costs averted would increase to $170,054 and $414,856, respectively (Perlman *et al.*, 2001). We therefore initiated a system in which an incentive of $25 was given to IDUs screened at the syringe exchange contingent on adhering to the referral for the screening chest x-ray within seven days. Adherence was 83% with use of the incentive compared with the 34% observed in the earlier cohort not receiving the incentive (p<.0001, OR = 9.1, 95% CI 3.9-22) (Perlman *et al.*, 2002).

Co-locating TB services on-site at drug treatment programs and at syringe exchange programs are valuable means of delivering these services to drug users in and out of drug treatment. Positively reinforcing incentives, particularly monetary incentives, appear to be both effective at increasing rates of adherence of drug users to TB services, and to be justifiable on a cost basis.

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INFECTIOUS DISEASES IN INJECTION DRUG USERS

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Injection drug users (IDUs) are at increased risk of several serious infections. A partial list of infections to which drug users are at significant increased risk is shown in table 1.

Human Immunodeficiency Virus (HIV):

It is appropriate that most attention has been directed at understanding the epidemiology and prevention of HIV infection and AIDS in drug injecting populations. The CDC estimates that about 775,000 cases of AIDS and 448,000 deaths have been reported in the United States between 1981 and 2000. In 1985 injection drug users accounted for about 20% of the AIDS cases in adults but this proportion increased to over 30% by 1994 (1). However, in the industrialized areas of the northeastern United States, the proportion of drug users among HIV/AIDS cases is even larger. In the State of Maryland the proportion of IDUs among the reported HIV/AIDS cases increased from about 25% in the early 1980s to 52% in 2000; in Baltimore the proportion had reached 62% in 2000 (2). In addition to the direct effects of injection drug use in the spread of HIV, many persons acquire HIV infection secondarily through sexual or other contact with persons who have acquired HIV through drug use. The

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proportion of HIV/AIDS cases in ethnic and racial minorities and women has increased substantially in the last decade. This increase is partially attributable to the direct or indirect effects of injection drug use.

Drug use also has been very important in the global HIV/AIDS pandemic. The emerging epidemics in several countries in Eastern Europe, the former Soviet Union, China, and Central Asia are primarily due to injection drug use. Over 172,000 HIV infections have been reported in Russia; most of these infections were reported in the last year or two. It is estimated that the actual number may be 5-10 times higher and over 80% of these infections have been linked to injection drug use (3). A dramatic example of the potential for rapid spread of HIV infection by illicit drugs occurred in Russia, where thousands of IDUs were infected with the identical strain of HIV because human blood contaminated with HIV had been added to the heroin, in order to "neutralize impurities", prior to its distribution (4). Beyrer and colleagues have traced several heroin distribution routes from the original opium source in northern Myanmar (Burma) by genetic sequencing of HIV isolates from infected IDUs living along these routes (5).

Several Asian countries, including Burma, China, Thailand, Malaysia, Viet Nam and northeastern India have experienced major HIV/AIDS epidemics due to injection drug use (6). In Thailand, epidemic spread of HIV was first recognized among drug uses in Bangkok in early 1988 (7). Semiannual sentinel surveys throughout Thailand subsequently found HIV prevalence rates of about 40% among drug using populations throughout the country (7). The extensive epidemic of sexually-transmitted HIV was largely controlled by a comprehensive public health program which included the promotion of condoms, especially for commercial sex, STD prevention and treatment, voluntary counseling and testing and other interventions designed to decrease the risks of sexually-transmitted HIV (8). Nevertheless, the proportion of HIV infections related to injection drug use has increased and remains an obstacle to further control of the Thailand epidemic (9, 10).

Despite the global expansion of HIV transmission involving drug users, which was recently estimated by WHO to involve 114 countries, several countries have implemented apparently effective prevention efforts in populations of IDUs (6). Australia has had one of the most extensive and successful harm reduction program to prevent HIV infections in IDUs (6). In addition, many countries in Western Europe and many cities in the United States have reported successful prevention programs. DesJarlais and colleagues reported lower HIV infection rates among IDUs in New York in recent years (11). The HIV incidence rates in IDUs enrolled in the ALIVE study in Baltimore have declined from 4.45 per 100 person years in 1988-1990 to 1.84/100 person years in 1995-1998 (12). Generally, the incidence of HIV has declined in recent years among drug users in large cities in the northeastern United States, as harm reduction, education and drug treatment programs have expanded.

Hepatitis C Virus (HCV):

Injection drug users are commonly infected with a number of pathogens, which are acquired parenterally. Infections with hepatitis C virus (HCV) may be the most frequent and widespread. Numerous studies among populations of IDUs have found HCV prevalence ranging from 60% to over 90% (13). Furthermore, incident infection with HCV often occurs in the first few months after initiation of injection drug use (14). With the advent of more effective therapy for HIV infection, clinical complications of HCV infection among IDUs have become more troublesome. Persons co-infected with HIV and HCV commonly experience more rapid progression of the hepatic complications of HCV (15). Whether HCV infections cause more rapid progression of HIV is less clear (16, 17). Nevertheless, there is growing recognition of the importance of diagnosing and treating both HIV and HCV infections, when indicated, when they occur among IDUs (18).

Other Hepatitis Viruses:

Infections of injection drug users with hepatitis B virus (HBV) are also very common (19). Therefore, IDUs should be offered HBV vaccine if they are still susceptible. Apparently, HBV infections have decreased in the United States in recent years with more widespread use of HBV vaccines in infants, children, adolescents and adults at high risk of infection.

A significant problem in screening drug users for their susceptibility to HBV is that a high proportion, about 25-30%, have antibodies to HBcore antigen without antibodies to HB surface antigen (19). The reason for this aberrant antibody profile is not entirely clear; however, there is some evidence that it may be related to co-infection with HCV, which is very common in IDUs (20). Nevertheless, this antibody pattern complicates the assessment of

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whether an IDU has previously been infected with HBV or is still susceptible and requires HBV vaccine (21). It is likely that in most cases "HBcore only" antibodies in an IDU signify a previous HBV infection. However, in persons at lower risk of HBV, such as volunteer blood donors, most "core-antibody only" tests are non specific and do not indicate the person has been infected previously with HBV (22)

Hepatitis A virus (HAV) infections are also common among IDUs and are most likely to have been acquired enterically (23). Because IDUs are at high risk of HAV infection, those who are susceptible should be given HAV vaccine. Superinfection of HCV or HBV carriers with HAV has been reported frequently to cause fulminant liver failure (24).

Hepatitis G virus (HGV) is a flavirus that was identified recently. Although HGV has some structural homology with HGV, it isn't a true "hepatitis" virus because it rarely causes hepatitis and doesn't replicate in the liver. Injection drug users are commonly infected with HGV (25). Considerable attention has been directed at HGV recently with reports that persons co-infected with HGV and HIV progressed more slowly to AIDS (26, 27). This viral interaction may partially explain why HIV infected drug users do not progress to AIDS more quickly than other persons with HIV infection (28-30).

Other Infections:

Injection drug users are at increased risk to a number of other infections. Bacterial infections, such as those due to staphylococci, streptococci, candida, or anaerobic organisms may result from contaminated injection practices. These infections may lead to cellulitis, phlebitis, endocarditis or infection of other organs.

Respiratory infections due to M. tuberculosis or S. pneumoniae also are common among IDUs. The interaction between these bacteria and HIV has been extensively evaluated in drug users and other populations. In reality, infectious disease risks in injection drug users are so common and complex that multiple chronic infections, which may interact with each other, should be expected in these populations. Some of these interactions have been discussed in this presentation.

TABLE 1: Some Common Infections to Which Injection Drug Users are at Significantly Increased Risk

INFECTION	CLINICAL MANIFESTATION
VIRUSES	
- HIV	AIDS
- Hepatitis C virus (HCV)	Hepatitis, (Acute & Chronic), Cirrhosis, Liver cancer, B-cell lymphoma
- Hepatitis B virus (HBV)	Hepatitis, (Acute & Chronic) Cirrhosis, Liver cancer
- Hepatitis A virus (HAV)	Hepatitis (Acute), Aplastic anemia (rare)
- HTLV I&II	Adult T-cell Leukemia, Chronic Myelopathy
- HHV-8	Kaposi's sarcoma
- HPV	Cervical cancer
BACTERIA	
- Staphylococci (Pneumococcus)	Abscesses, Phlebitis, Endocarditis
- Streptococcus pyogenes	Sepsis, Cellulitis,
- Anaerobic bacteria	Cellulitis, Sepsis
- M. tuberculosis	Tuberculosis
FUNGI	
C. neoformans	Pneumonia, Meningitis
Candida species (esp HIV+)	Orophargnsitis, Esophagitis, Pneumonia, Sepsis
Pneumocystis carinii (esp HIV+)	Pneumonia

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SYMPOSIUM VI

UNDERSTANDING THE ABUSE-RELEVANT EFFECTS OF DRUGS: STUDIES BY YOUNG INVESTIGATORS

P.W. Czoty and K.M. Wilcox, Chairpersons

The purpose of this symposium was to provide a forum for productive young researchers in the field of drug abuse to present and discuss results of their recent studies. To create a niche for oneself, a young investigator must be innovative by initiating a line of research that contributes greatly to the understanding of the clinical bases of drug abuse. One approach to is to critically examine the preclinical models presently being used to study different aspects of drug abuse and to advance these techniques by addressing clinically-relevant variables not currently accounted for by experimental models. Alternatively, an investigator may examine a collection of related variables with complementary techniques to gain a greater insight regarding the relationship among the consequences of drug effects at different levels of analysis. To this end, three speakers discussed the techniques they use to gain a unique perspective on the behavioral effects of abused drugs. The symposium began with a discussion of the effects of local anesthetics on dopamine transporter occupancy, elevations in extracellular dopamine and reinforcing effects in rhesus monkeys. Employing PET imaging, in vivo microdialysis and schedule-controlled behavior concurrently provides greater insight into the role of the dopamine transporter in mediating the reinforcing effects of drugs than can be gained when these techniques are used separately. Additionally, studies conducted in rhesus monkeys examined the contribution of time course of effect in determining the reinforcing strength of cocaine and methylphenidate analogs. Many traditional assays used to assess a drug's reinforcing strength fail to account for this variable. Finally, the effects of general anesthetics were studied in a human laboratory model. Although inhalant abuse is widespread, the difficulty inherent to its study has caused investigation of the behavioral pharmacology of this drug class to be limited in preclinical models. Overall, these presentations exemplify the ways that current models of factors that underlie vulnerability to abuse drugs are advanced through the efforts of innovative young investigators.

RELATIONSHIP BETWEEN THE DOPAMINE TRANSPORTER AND THE REINFORCING EFFECTS OF DOPAMINE TRANSPORTER INHIBITORS IN RHESUS MONKEYS

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Illicit cocaine use is wide spread in the United States. It is important to understand the pharmacological mechanisms modulating the behavioral effects of cocaine relevant to its abuse, to aid in the development of therapeutic compounds to treat cocaine abuse. To achieve this goal, research efforts should focus on both the neurochemical and the behavioral mechanisms controlling cocaine use. It is well established that cocaine binds to biogenic amine transporters located within the membranes of neurons, and inhibits the reuptake of released dopamine, norepinephrine and serotonin (Heikkila *et al.*, 1973; Horn, 1990; Madras *et al.*, 1989; Ross and Renyi, 1969). The dopaminergic mechanisms of cocaine are thought to play a central role in its reinforcing effects (Kuhar *et al.*, 1991; Woolverton and Johnson, 1992). A positive correlation has been found between dopamine transporter affinity and self-administration potency for several dopamine uptake inhibitors, including cocaine (Ritz *et al.*, 1987; Wilcox *et al.*, 1999). However, there are limitations to correlating the *in vitro* and *in vivo* effects of drugs. *In vitro* assays do not mimic the physiological conditions present in an intact animal (i.e., blood-brain barrier, drug metabolism) which may affect the amount of drug available to interact with its site of action *in vivo*. In addition, it is difficult to determine the precise *in vitro* concentration that would be relevant *in vivo*. Therefore, the purpose of the present study was to compare the reinforcing and neurochemical effects of dopamine transporter ligands *in vivo*. Specifically, the relationship between reinforcing effects, dopamine transporter occupancy in the striatum, and increases in extracellular dopamine in the caudate nucleus as a consequence of drug administration was studied.

The dopamine transporter ligands evaluated in the present study were local anesthetics. Some local anesthetics effectively maintain i.v. drug self-administration in monkeys. In addition, dopamine transporter affinity and potency to inhibit dopamine uptake *in vitro* are related to the reinforcing effects of local anesthetics in monkeys (Wilcox *et al.*, 1999; 2000). Importantly, the local anesthetics examined in the present study had similar pharmacokinetic profiles; therefore, differences between compounds could be better attributed to their pharmacodynamic profiles (i.e., dopamine transporter effects). The reinforcing effects of cocaine, dimethocaine and procaine were examined under a second-order schedule of reinforcement. Rhesus monkeys (n=3) were trained to respond under a second-order schedule for injections of cocaine (0.10 or 0.17 mg/kg/inj). When responding was stable, cocaine (0.003-1.0), and the local anesthetics dimethocaine (0.03-1.7) and procaine (0.10-10) were substituted for the usual daily dose of cocaine. Cocaine and dimethocaine maintained similar response rates in two of the three monkeys tested. Response rates for dimethocaine were greater than for cocaine in the third monkey. Procaine maintained lower response rates compared to cocaine in all three monkeys tested.

To characterize further the pharmacological mechanism of the reinforcing effect, percent occupancy of the dopamine transporter was examined in rhesus monkey striatum using positron emission tomography neuroimaging techniques. The level of dopamine transporter occupancy appears to be important in determining the reinforcing effects of cocaine and other dopamine transporter ligands (Volkow *et al.*, 1996; 1997). Dopamine transporter occupancy was determined by displacement of 8-(2-[18F]fluroethyl)2b-carbomethoxy-3b-(4-chlorophenyl)nortropane (FECNT). At doses that maintained maximum response rates, dopamine transporter occupancy was between 65-76% for both cocaine and dimethocaine, and between 20-41% for procaine. Maximum response rates under the second-order schedule were consistent with percent dopamine transporter occupancies for cocaine, dimethocaine and procaine.

Previous studies reported that cocaine and procaine increased extracellular striatal dopamine in rats measured using *in vivo* microdialysis (Woodward *et al.*,1995). The potency order for cocaine and procaine to increase dialysate dopamine was consistent with their potencies as reinforcers, and their potencies to inhibit dopamine uptake (Woodward *et al.*, 1995; Woolverton, 1995). Increases in extracellular dopamine were determined using *in vivo* microdialysis techniques in awake rhesus monkeys for two reinforcing doses of cocaine (0.10 and 1.0 mg/kg, i.v.), and compared to dopamine transporter occupancies at the same doses. Guide cannula were implanted bilaterally into the caudate nuclueus under sterile conditions. During surgery, the monkey was positioned in a stereotaxic frame, and coordinates were derived from the monkey's own MRI. There was a dose dependent elevation in extracellular dopamine over baseline levels. The lower dose of cocaine (0.10 mg/kg) increased extracellular dopamine 190% over baseline values, whereas, the higher cocaine dose (1.0 mg/kg) increased extracellular dopamine 320% over baseline values. Percent dopamine transporter occupancy was 55% and 89% for 0.10 mg/kg and 1.0 mg/kg cocaine, respectively. Increases in extracellular dopamine were consistent with dopamine transporter occupancy for the two doses of cocaine.

The above data support further the role of the dopamine transporter in the reinforcing effects, and therefore abuse liability of dopamine transporter ligands like cocaine. Specifically, binding to the dopamine transporter and increasing extracellular dopamine are important mechanisms. In addition, the underlying neurochemical mechanisms of a behavioral effect can be reliably determined using *in vivo* measures.

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THE ROLE OF DURATION OF ACTION AND SELECTIVITY FOR MONOAMINE TRANSPORTERS IN DETERMINING THE REINFORCING EFFICACY OF PYSCHOSTIMULANTS

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Drug self-administration in animal models of drug addiction has allowed for the systematic assessment of the determinants of drug-reinforced behavior. While these studies have yielded an abundance of information regarding the neurobiology of psychostimulant use, the complex interaction of the variables that influence the reinforcing strength of these drugs are still not fully understood.

Both pharmacokinetic and pharmacodynamic factors have been shown to mediate the strength, or efficacy, of a drug to maintain self-administration. For example, a recent study demonstrated three NMDA antagonists with different onsets of action differed in their relative reinforcing efficacy. In contrast, data from two laboratories that compared the reinforcing effects of several opiates with different half-lives indicated that duration of action did not influence their efficacy as reinforcers (Ko *et al.*, 2002, Panlilio and Schindler 2000) when compared using progressive-ratio (PR) schedules. With regards to the pharmacodynamic profile of psychostimulants, there is evidence that dopamine (DA) reuptake inhibition mediates the ability of these drugs to maintain responding (Wise 1998), whereas increased serotonin (5-HT) neurotransmission acts as a negative modulator of their reinforcing effects (Carroll *et al.*, 1990, Loh and Roberts 1990). However, the interaction of these two monoamines in mediating the reinforcing efficacy of psychostimulants is a relatively unexplored topic (but see Roberts *et al.*, 1999).

Responding under PR schedules has been used as an index for evaluating the relative strength of a reinforcing stimulus, including drug injections (Hodos and Kalman 1963, Stafford *et al.*, 1998). Under the conditions of a PR schedule, drug delivery is contingent upon the completion of successively increasing ratio sizes; the number of responses necessary for reinforcement is systematically increased until the animal stops responding (termed its "breaking point"; BP). In this study, a PR schedule was used to investigate the role of pharmacodynamic and pharmacokinetic variables in mediating the reinforcing efficacy of psychostimulants using several methylphenidate (MP) analogs and metabolically stable cocaine analogs with different durations of action and varied selectivity for the DA transporter (DAT) and 5-HT transporter (5-HTT) (Table 1).

Ten individually-housed adult, male rhesus monkeys implanted with chronically indwelling i.v. catheters were trained to respond under a within-session, exponentially-increasing PR schedule of cocaine reinforcement. For this study, the BP was defined as the final ratio completed when 2 hours had elapsed without an injection delivered. Therefore, session length was determined by the animal's performance. When responding maintained by the baseline dose of cocaine was stable (±20% of the mean number of injections for three consecutive sessions, with no trends in responding), saline and various doses of cocaine, MP and five analogs of these two psychostimulants (See Figure 1 for dose ranges) were made available for self-administration. Each drug was tested in 4 animal, with the exception of HDMP-28, which had not been completely determined at the time of this submission. Each dose of drug was available for at least 5 days and until responding was stable, and there was a return to base line between test doses.

Table 1. Pharmacokinetic and pharmacodynamic[a] profile of cocaine and methylphendiate analogs selected for self-administration under the PR schedule.

Compound	***Selectivity***[b]	**5-HT K_i (nM)**[c]	**DA IC_{50} (nM)**[d]	***Duration of action***[e]
cocaine	Mixed action (DA)	302	173	
Methylphenidate (MP)	Dopaminergic	>10,000	164	moderate
HDMP-28	Mixed action (DA)	26.8	11.1	moderate
HDMP-29	Serotonergic	2.5	465	moderate
PTT (WF-11)	Dopaminergic	131	8.2	long
WF-23	Mixed action (DA)	0.39	0.12	long
WF-60	Serotonergic	0.1	15.8	long

[a] DAT and 5-HTT binding affinity data for cocaine and cocaine analogs have been published previously (Bennett *et al.*, 1995). Data on the binding affinity of MP and MP analogs were obtained via personal communication with S. R. Childers, 2001.

[b] (DA) under the Selectivity column indicates that while the listed compound is relatively non-selective for the DAT versus the 5-HTT, it has a higher affinity for the DAT.

[c] IC_{50} values for cocaine and MP analogs at displacing [^{125}I]RTI-55 binding in rat striatal membranes

[d] K_i values for cocaine and MP analogs at displacing [^{3}H]paroxetine binding in rat frontal cortex membranes.

[e] Duration of action as compared to cocaine based on behavioral and neurochemical data (Daunais *et al.*, 1998, Hemby *et al.*, 1995, Nader *et al.*, 1997, Volkow *et al.*, 1995).

Responding decreased to low levels when saline was substituted for the training dose of cocaine; on average, fewer than 2 saline injections were self-administered when responding had stabilized (Figure 1). When various doses of cocaine, MP and their analogs were made available for self-administration, each of the seven drugs functioned as reinforcers in at least two of the four animals tested, but varied in their maximum efficacy to maintain responding (Figure 1). The rank ordering of the peak BPs for these seven drugs was: cocaine ≥ MP ≥ HD-60 = HDMP-28 ≥ PTT > HD-23 > HDMP-29.

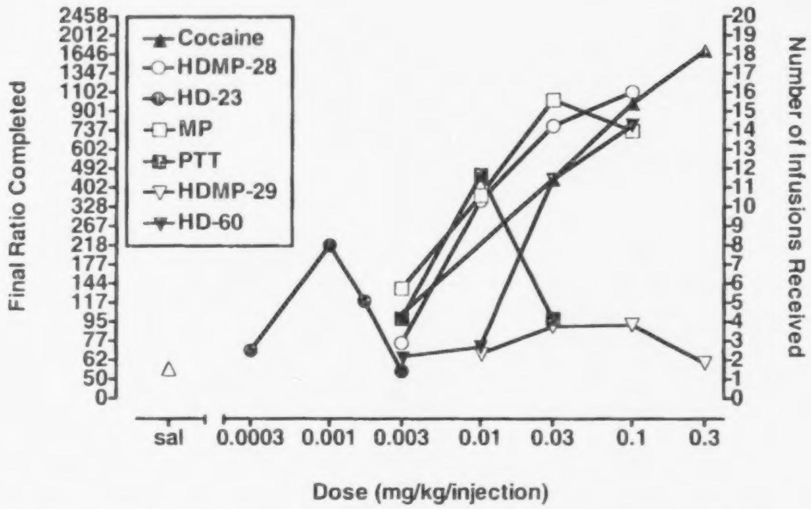

Figure 1. Final ratio requirement completed (breaking point, BP; left ordinate) and number of injections received (right ordinate) when various doses of each of the cocaine and methylphenidate analogs were substituted for the training dose of cocaine. "sal" denotes BP and number of injections self-administered when saline was substituted for the base-line dose of cocaine. Each point represents the mean of the last 3 sessions across animals under each condition.

These data indicate that duration of action does not influence the reinforcing efficacy of psychostimulants, extending the findings from previous studies with opiates. In addition, there appeared to be a positive relationship between the affinity of these drugs for the DAT and their potency to maintain self-administration behavior, also in agreement with what has been published previously (Bergman *et al.*, 1989, Ritz *et al.*, 1987, Wilcox *et al.*, 1999). However, this relationship may have been influenced by 5-HTT binding as well, consistent with the hypothesis that increased 5-HT neurotransmission acts as a negative modulator of dopaminergic activity (Czoty *et al.*, 2002). Furthermore, these data suggest that there is a range of DAT affinity in which responding is maximally maintained in that the compounds with the highest and lowest affinity for the DAT (HD-23 and HDMP-29, respectively) maintained the least amount of behavior. Like the relationship between DAT affinity and behavioral potency, the range of DAT affinity and efficacy to maintain responding also seems to be modulated by 5-HT reuptake inhibition. Finally, these data contrast with the results from a previous study that demonstrated a positive correlation between the ratio of 5-HT/DAT binding affinity and the efficacy of a series of cocaine analogs (including the three analogs tested here) to maintain self-administration in rodents responding under a similar PR schedule (Roberts *et al.*, 1999). While the reasons for this are not completely clear, these discrepant results illustrate the necessity of using multiple species when studying the interactions between drugs and behavior. Overall, these findings place more emphasis on the pharmacodynamic properties of a drug in determining its reinforcing efficacy.

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REINFORCING AND SUBJECTIVE EFFECTS OF INHALED ANESTHETICS IN HUMANS

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Inhalant abuse is a significant worldwide public health problem that has received relatively little attention from the scientific community. In particular, there is a lack of research on the behavioral pharmacology of inhalants in humans. The present two studies are part of a program of research designed to establish a human laboratory model of inhalant abuse. This laboratory model consists of studying the reinforcing and subjective effects of inhaled general anesthetics in non-drug-abusing humans. We study reinforcing and subjective effects because they are relevant to drug abuse. We study inhaled general anesthetics because they 1) are abused and 2) resemble other frequently abused inhalants, such as glue or paint, that cannot be safely or ethically administered to humans in the laboratory. By studying a gaseous anesthetic, nitrous oxide (N_2O), and volatile anesthetics, such as sevoflurane, we are studying the abuse-related effects of two of the three classes of abused inhalants, according to Balster's (1998) classification. The present two studies examined the reinforcing and subjective effects of N_2O (Study 1) and sevoflurane (Study 2).

Healthy adults (21-39 years old) with no self-reported history of drug dependence were fitted with an anesthesia mask, which was placed over their nose and mouth. In Study 1, 20 non-drug-abusers sampled 0, 10, 20, 30, and 40% N_2O in separate sessions, as well as 100% O_2 (placebo), for 10 min each, in randomized order. The agents were identified by letter code, so that subjects and the research technician were blind to the drug and dose being sampled. A 30-min recovery period (mask off) followed each sample. After the second sampling period, the mask

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as replaced, and subjects chose nine times, once every 5 min, among N_2O (e.g., "Agent A"), O_2 (e.g., "Agent B"), r "neither" (also O_2). A 1-h recovery period followed the 45-min choice period. Study 2 was identical, except for ample size (n=13, to date) and anesthetic (0, 0.2, 0.4, 0.6, and 0.8% sevoflurane). Subjective effects were assessed luring sampling and recovery periods, and at the end of the session (1 h after the choice period). Subjective-effects neasures took the form of visual analog scales (VAS), Likert scales, and an inhalant effects checklist.

Although both studies found individual differences in reinforcing effects, mean N_2O choice increased as a function of dose, whereas mean choice of sevoflurane was an inverted U-shaped dose-response function. Both anesthetics produced dose-related increases in ratings of drug effect strength, drug liking and wanting (with ratings of liking and wanting being higher for N_2O than for sevoflurane), and several VAS items (e.g., high, lightheaded, tingling, dreamy, coasting, floating, difficulty concentrating). Both anesthetics increased scores on several scales of the inhalant effects checklist (e.g., body awareness, time perception, euphoria, changes in sensation/perception) and decreased VAS ratings of "in control of thoughts" and "in control of body." The drugs produced somewhat different profiles of effect: N_2O, but not sevoflurane, increased ratings of "stimulated," and sevoflurane, but not N_2O, increased ratings of "sedated," heavy/sluggish," and "nauseated." Correlations between choice and subjective effects rated during the sample were weak ($p>0.05$); however, ratings of drug liking and wanting obtained after the session were positively correlated with anesthetic choice ($p<0.05$).

The present data show the choice procedure to produce orderly, dose-related reinforcing and subjective effects of inhaled anesthetics in non-drug-abusing humans. The data suggest that N_2O has more abuse liability than sevoflurane, at least in this subject population, as indicated by the higher ratings of drug liking and wanting of N_2O, as well as the monotonic, increasing dose-choice function for N_2O, compared with the inverted U-shaped dose-choice function for sevoflurane. The differences in subjective effects of the two anesthetics are consistent with Balster's (1998) suggestion that the two types of anesthetics represent different classes of abused inhalants. The fact that subjective effects rated while subjects are under the influence of a drug are less correlated with choice than retrospective ratings has been reported by other investigators (e.g., Roache *et al.*, 1989).

We conclude that the choice procedure is useful for studying abuse-related effects of inhaled anesthetics and is, therefore, a useful human laboratory model of inhalant abuse.

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SYMPOSIUM VIII

PRESCRIPTION DRUG ABUSE: WHAT DO WE KNOW?

S. Schnoll and F. Sapienza, Chairpersons

THE EPIDEMIOLOGY OF PRESCRIPTION DRUG USE

E. H. Adams

INTRODUCTION

Understanding the size of the prescription drug abuse problem is important from a number of perspectives: estimating the impact of prescription drug abuse on the nation's health; estimating treatment need; identifying risk factors for abuse/dependence; and understanding the risk of abuse/dependence/addiction in patient populations. This paper focuses primarily on estimates of abuse/dependence/addiction in patient populations. This is a critical issue because fear of addiction by physicians and patients can contribute to the continued under-treatment of pain.

DRUG ABUSE IN THE GENERAL POPULATION

In recent years both the Epidemiology Catchment Area Study and the National Comorbidity Study (NCS) have attempted to measure the prevalence of various psychiatric conditions including estimates of drug abuse and dependence in the general population. The National Household Survey on Drug Abuse (NHSDA) first added questions on the problems associated with prescription drug use in 1985 and generated estimates of treatment need in 1988 based upon reported problems. The NHSDA approach to estimated treatment need has been refined continuously since then. The National Comorbidity Study was fielded between September 1990 and February 1992. It was designed as a stratified multistage area probability sample of persons aged 15 to 54. The sample of 8,094 was released in replicates so that each represented a national probability sample. Drug questions were included from the NHSDA and the Comprehensive International Diagnostic Interview (CIDI) and DSM-IIIR™ criteria were applied to estimate abuse and dependence.

The 12-month estimate of drug dependence was 1.8 percent. Estimates by prescription drug class are shown in Table 1.

Estimated Prevalence of Extramedical Use and Dependence in Study Population and Lifetime Dependence Among Users

	History Of Dependence		**History of Extramedical Use**		**Dependence Among Extramedical Users**	
Drug Class	**P**	**SE**	**P**	**SE**	**P**	**SE**
Analgesics	**0.7**	0.1	**9.7**	0.5	**7.5**	1.0
Anxiolytics	**1.2**	0.2	**12.7**	0.5	**9.2**	1.1
Stimulants	**1.7**	0.3	**15.3**	0.7	**11.2**	1.6

Source: Anthony, J.C., Warner, L.A., Kessler, R.C. Experimental & Clinical Pharmacology, 1994. Vol 2, No. 3, 244-268

The NHSDA is an ongoing survey of the household population of the United States. It has been conducted since 1971. In the last 10 years the sample has grown from 5,600 TO 70,000. The NHSDA for the year 2000 included 71,764 selected representatives of the non-institutionalized population of the United States aged 12 and older. Data are collected for lifetime, past year and past month use of drugs. This includes illicit drugs as well as licit

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psychotherapeutic drugs. Data are collected on drug dependence and withdrawal and attempts at estimating treatment need are based upon dsm-iv™ criteria.

A study of the concordance between the NCS and the NHSDA data was done using NHSDA data from 1991 to 1993 among persons aged 18 to 44 years old. The estimate from the NHSDA was 1.8 percent compared to 2.0 percent for the NCS.

ABUSE IN PATIENT POPULATIONS

For more than 30 years the literature has documented the problem of unrelieved pain in patient populations. While ignorance of how to appropriately treat pain is part of the problem fear of addicting patients on the part of physicians is also a significant issue. Patient fears of becoming addicted compound the problem. This raises two questions: (1) How serious is the problem of addiction in patient populations; and (2) What is the best way to measure it?

Fishbain (1992) reviewed 24 articles on the subject of dependence/addiction in chronic pain patients. The estimates of the diagnosis of drug abuse/dependence/ addiction ranged from 2.2 to 18.9 percent. However, only 7 studies utilized acceptable diagnostic criteria. Another study using data from the Boston Collaborative Study found 4 cases of addiction in 11,882 hospitalized patients without a history of addiction (Porter and Jick, 1980). Similarly, Perry and Heidrich (1982) found zero cases among 10,000 burn patients. Perhaps the issue of problems with measurement is best highlighted by studies conducted by Chabal *et al.*, (1997) and Zenz in 1992. Chabal's patients were considered abusers if they met 3 criteria that essentially measured attempts to obtain analgesics. This study was conducted in a holistic program and low does of methadone (mean 4 mg) were given. The rate of abuse was 28 percent. In the Zenz study, the analgesic dose was increased until adequate pain relief was achieved. In this study, no addictive behaviors were found.

It is clear that the conditions of the study can affect the outcome. However, a larger question may be the adequacy of accepted diagnostic criteria in patient populations. The DSM-IV™ criteria include tolerance, withdrawal, giving up important social occupational or recreational activities, and a great deal of time spent in activities necessary to obtain the substance. In patient populations these criteria may be irrelevant or worse, misleading. Tolerance and withdrawal are an expected consequence of chronic opioid therapy and are not indicative of addiction in patient populations (Aronoff, 2000). In chronic pain populations, opioid use may lead to increased levels of functioning not impaired functioning (Sees & Clark 1993).

Compton has developed a screening tool that includes a number of behaviors that may be related to addiction. These include increasing analgesic dose/frequency, patient believes that he/she is addicted, history of addiction, multiple prescription sources, MD/DDS limited care, and use of analgesics for other symptoms (Compton, Darakjian, and Miotto 1998)

CHRONIC PAIN PATIENTS

In this study the issue was to evaluate the abuse potential of tramadol, an unscheduled analgesic intended for the treatment of chronic pain.. An algorithm based upon four dimensions was developed to assess possible abuse. The dimensions include:

1. Inappropriate Use
2. Use to Produce Intoxication
3. Inability to Stop Use
4. Evidence of Opioid Withdrawal

Tramadol was compared to a negative comparator NSIADs,and hydrocodone containing analgesics, drugs with recognized abuse potential. A total of 11,352 subjects were recruited into the study and either prescribed tramadol directly or randomized to one of two treatment arms (tramadol vs. NSAIDS or tramadol versus hydrocodone). Subjects were interviewed 9 times over a 12-month period using computer assisted telephone interviewing (CATI) techniques. A total of 87,180 interviews (85%) were completed. The proportion of positive cases on the abuse index (hitting at least once) was hydrocodone (4.87), tramadol (2.69), and NSAIDS (2.55). The abuse levels associated with NSAIDs and tramadol were significantly lower than those associated with hydrocodone containing analgesics.

DISCUSSION

The literature on abuse and dependence in patients with chronic pain is problematic because many studies do not use acceptable diagnostic criteria. Furthermore, in chronic pain patients, DSM-IV™ based criteria may be inappropriate. This raises the issues of how to measure abuse and dependence in these populations.

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A POST-MARKETING SURVEILLANCE PROGRAM TO MONITOR ULTRAM® (TRAMADOL HYDROCHLORIDE) ABUSE IN THE UNITED STATES

T.J. Cicero, E.H. Adams, A. Geller, J.A. Inciardi, A. Muñoz, S.H. Schnoll, E.C. Senay, and G. E. Woody

INTRODUCTION

In 1994, Ortho-McNeil Pharmaceutics (OMP) proposed to market tramadol in the United States as a non-scheduled prescription drug with the trade name Ultram™ based upon clinical epidemiology in Europe where abuse of the compound was very low despite over 20,000,000 patient exposures worldwide. At the Drug Abuse Advisory Committee (DAAC) meeting of the FDA on August 3, 1994, the DAAC unanimously concurred that Ultram™ had a relatively small abuse potential, based on the eight-factor analysis required under the Controlled Substance Act (CSA), and thus could be marketed as a non-scheduled drug. Moreover, the DAAC believed that the development of new analgesics for the treatment of pain addressed an extremely important public health problem: the acknowledged under-treatment of pain which, at least in part, could be due to the reluctance of physicians to prescribe scheduled analgesics. Thus, after careful consideration, based on the risk-benefit analysis mandated by the CSA, the DAAC unanimously recommended that Ultram™ not be scheduled. However, the DAAC was justifiably worried that a significant problem with abuse of Ultram™ might occur and become widespread long before it was actually recognized utilizing DAWN or MedWatch data alone.

To address these valid concerns, OMP pledged that a comprehensive post-marketing surveillance program would be developed and overseen by an Independent Steering Committee (ISC) to provide an early warning signal of any unexpectedly high abuse of Ultram™. The appointment of the ISC was key in the DAAC and FDA's decision because it was given the power by the FDA and OMP – an unprecedented step – to oversee the marketing experience with Ultram™ and to recommend scheduling if unexpectedly high levels of abuse were found. This committee established a proactive post-marketing surveillance program under its direct supervision, which was designed to provide the detection, at a very early stage, of any wide spread abuse of Ultram™. The ISC consisted of the authors of this paper (TJC, Chairman).

The most important element of this program was the establishment of an extensive network of drug abuse experts consisting of NIDA grantees and other individuals with significant contact with drug abuse prone populations ("key informants"). Reports of abuse that were received from the company (spontaneous reports) and from the quarterly surveys were reviewed by the ISC and rated as positive, possible, alleged or negative for abuse or defined by DSM IV.

RESULTS

A tabulation of the reports showed the most frequent report was of typical and atypical withdrawal upon discontinuation of tramadol (32.8% of the total) with no indication of abuse, followed by positive and possible for abuse (30.4%), negative (18.5%) and alleged (18.3%). Using DSMIV criteria, only 11.7% and 3.0% of all cases were rated as positive for drug dependence and abuse, respectively.

The distribution of all reports by the source - OMP or the ISC - revealed that over 50% of the cases judged positive for abuse resulted from the surveillance efforts, as opposed to spontaneous reports. The number of spontaneous reports has gradually declined over the 7-year period while ISC generated reports have remained stable so that the vast majority of cases now are generated by the ISC.

During the first two quarters after tramadol's introduction, there was no evidence of abuse. Thereafter, reports of abuse increased, reaching a peak in the first three quarters of 1996 of approximately two cases per month per 100,000 patients. Subsequently, despite continuously active surveillance efforts, the rate had decreased significantly (P=0.011) to approximately 0.5 1.0 cases per month for 100,000 patients over the year ending December 31, 2001.

Histories of drug/alcohol abuse were available in 77% of all abuse/dependence cases. In 97.3% of these, there was a history of opiate, alcohol, or other drug abuse. Importantly, the ISC has found no cases of drug-naive patients prescribed Ultram™ for pain who subsequently began to abuse it. Thus, despite "conventional wisdom", these data support the general clinical experience that pain patients rarely abuse their prescribed medications.

The abuse of tramadol was confined to isolated pockets across the country and, most significantly, was transient in nature: abuse cases appeared rather quickly in clusters in a particular city and dissipated just as rapidly. It is important to note that cases of continuing abuse in a given region were virtually non-existent. One of the more striking features of the patterns of abuse of tramadol was that high levels of abuse were not detected in areas where heroin and other drug use is prevalent: the northeastern corridor of the United States (Washington to Boston), South Florida, Detroit, Chicago, and Los Angeles. Rather its use seemed to be confined to areas where availability of heroin and other alternative drugs was low. This suggests, as documented by our key informants and personal interviews with drug users, that tramadol rates low as an alternative to heroin, if heroin and more powerful substitutes are equally available.

DISCUSSION

The ISC concludes that the surveillance program described in this paper met the objectives of the `safety net' the DAAC required in making its recommendation to not schedule tramadol in 1994: it has been proactive and timely in soliciting and reporting cases of abuse with sufficient sensitivity to stratify abuse by geographic location; and methods were developed to characterize abuse which permitted the implementation of apparently successful intervention strategies to reduce abuse. The ISC concludes that the rates of abuse of tramadol have been low (<1.0 cases per 100,000 patients prescribed the drug) and consistent with prior pre-clinical, clinical and epidemiological experience with this drug world-wide. Moreover, it can be argued that the non-scheduled status of the drug combined with this surveillance program has made possible the appropriate prescribing of an analgesic with low abuse potential, thus benefiting public health.

The most striking feature of these data gathered by the ISC was the very restricted pattern of abuse observed with tramadol. Nearly all of the cases could be traced to 8 10 locations nationwide. The ISC was struck by the almost total absence of abuse/dependence in the country's largest cities with substantial populations of street addicts, such as New York, Philadelphia, Chicago, Detroit, Miami, and Los Angeles. Since these areas also had some of the highest sales of tramadol and number of patient exposures, the relative availability of tramadol cannot explain this phenomenon; rather, the ISC postulates, based upon information from the key informant network, that the absence of wide-spread street abuse in these areas is due to the low euphorigenic properties of tramadol in comparison to other drugs that are more readily available.

PRESCRIPTION DRUG DIVERSION

J.A. Inciardi

Prescription drug diversion involves the unlawful movement of regulated pharmaceuticals from legal sources to the illicit marketplace. In the 1990s, the Drug Enforcement Administration (DEA) estimated that the diversion and illegal trafficking in prescription drugs was a $25 billion-a-year industry. The most common mechanisms of diversion include: the illegal sale of prescriptions by physicians; the illegal sale of prescriptions by pharmacists; "doctor shopping" by individuals who visit multiple physicians to obtain prescriptions; theft, forgery, or alteration of prescriptions by patients; and, robberies and thefts from pharmacies and thefts of institutional drug supplies. Diversion involving physicians is typically the result of: "deceived doctors," through deceptions or "scams" by their patients; "dated doctors," because of their outdated medical knowledge and lax prescription writing practices; "disabled doctors," who are impaired by their own problems with drug and alcohol problems; and, "dishonest doctors" – the so-called "script docs" who write prescriptions for a fee.

Methods for studying the extent of the diversion of prescription analgesics were developed as part of a large scale post-marketing surveillance study of tramadol hydrochloride (Ultram). The research was supported by Ortho-McNeil Pharmaceutical, and included in-depth studies in Cincinnati and Columbus, Ohio, where the diversion of tramadol was alleged to be high, as well as quarterly surveys of a national sample of drug diversion investigators. In the two Ohio studies, data were extracted from police files on a monthly basis, with data collection and analysis accomplished through an unrestricted research grant from Ortho-McNeil Pharmaceutical to substance abuse researchers Wright State University School of Medicine.

In Cincinnati, from January 2001 through December 2001, a total of 304 cases were handled by the police diversion unit. Among these, oxycodone products were "mentioned" as diverted or allegedly diverted in 190 cases, followed by hydrocodone (147), benzodiazepines (124), and propoxyphene (33). Tramadol was mentioned in 28 cases, and in only 32.1% of these was tramadol actually diverted. In Columbus during the same period, a total of 106 cases were handled by diversion investigators. Among these, hydrocodone products were "mentioned" as diverted or allegedly diverted in 54 cases, followed by oxycodone (23), benzodiazepines (14), and carisoprodol (12). Tramadol was diverted in only 4 cases.

The national diversion survey involved quarterly questionnaires to police offiecers involved in pharmaceutical diversion investigations. During 2001, a total of 85 investigators were contacted and completed questionnaires were received from a mean of 34 investigators each quarter. Based on their responses, a total of 5,802 cases of pharmaceutical diversion were reported. Among these, there were 1,795 hydrocodone mentions, followed by oxycodone (701), alprazolam (371), diazepam (201), codeine (171), carisoprodol (151), propoxyphene (68), and tramadol (61).

All three surveys documented the diversion of tramadol to be extremely low: 1% of the cases in the national survey; 2.9% of the cases in Cincinnati; and 3.7% of the cases in Columbus. In the overwhelming majority of cases where in-depth information was available, the diversion of tramadol occured in combination with numerous other drugs, such as oxycodone, hydrocodone, and diazepam. The majority of investigators did not consider the diversion of tramadol to be a significant problem in their jurisdictions. For the 2002 national survey, focused efforts are being made to expand the number of diversion reporters throughout the United States.

OXYCONTIN®: MYTH VERSUS REALITY

S.H. Schnoll

Prescription drug abuse has been an issue for over a century. Major drug laws like the Pure Food and Drug Act, the Harrison Narcotics Act, the Marijuana Tax Act, and most recently, the Controlled Substances Act all passed with the intention of reducing the abuse of prescription drugs. Despite the long history of concern over this issue, there are few studies that provide a clear picture of the nature and scope of the problem of prescription drug abuse. Periodic media reports will single out one drug or another as a major problem, often with little data to support the allegations. These reports often have the effect of increasing interest in the drug rather than decreasing it. "The media appear neither to know nor to care that such hyperbole can be counterproductive, encouraging drug users to add the new substance to their repertoires. The act of defining a new drug of choice, an ultimate high, a hot drug, may lead potential users to ask themselves why they are not sufficiently fashionable to have experienced it." (Jenkins, 1999)

Previously, extensive media attention was directed at "Ts and blues" and Rohypnol. In both cases, the problem was confined to limited geographic areas, but received wide media attention that gave the impression that it was a national problem. Very few studies were able to actually identify Rohypnol as present in the United States to any major extent, and the Ts and blues problem was related to the scarcity of heroin in the areas where it occurred with the problem disappearing when heroin returned. (Reed and Schnoll, 1986)

Recent media stories about OxyContin have described high rates of abuse in communities that apparently had no such problems in the past and that there has been a rash of overdoses related to the drug. Evaluation of these reports show that these communities have had significant problems with prescription drug abuse that predated the abuse of OxyContin, and that the abusers where overwhelmingly multiple substance abusers who have had a long history of substance abuse with OxyContin being a recent choice. The overdose and death data have been equally misleading. The majority of cases have multiple substances present in their systems making it difficult to identify a single substance as the offending agent. Some articles have described OxyContin as the most frequently prescribed prescription pain medication on the market. Data from IMS Health's prescription audit for 2001 show that OxyContin accounts for only 4.1% of prescription opioid analgesics compared to hydrocodone which accounts for over 47% of prescription opioid analgesics. Even among oxycodone products, OxyContin only accounts for 27.1% of the prescriptions.

There are 2 major reasons to analyze prescription drug data: to examine whether and to what extent abuse and deaths involve unsafe and inappropriate use of prescription drugs by legitimate patients and/or inappropriate prescribing by physicians; and, to explore the extent, and circumstances under which prescription drugs are involved in the deaths of drug abusers. The results of such analyses should serve a medical or public health purpose such as enabling the manufacturer to change labeling or correct inappropriate prescribing practices, and/or enabling law enforcement and public health officials to intervene to prevent diversion and abuse.

Non-medical use of prescription analgesics appears to be rising based on NHSDA and DAWN data. Specific analyses of the NHSDA data indicate that among life-time users of OxyContin 97.4% abused other analgesics, 94.3% abused 2 or more other analgesics, 68.4% used heroin or cocaine, and 68.7% used methamphetamine or Ecstasy demonstrating that the majority of OxyContin abusers are multiple drug abusers of both prescription and illicit drugs.

Studies of medical examiner data should determine whether the cause of death was by one or more drugs and whether the death was drug induced (directly caused by an overdose) or drug related (drug abuse was a contributing factor, but not the immediate or sole cause.) In drug induced deaths when more than one drug is present, it cannot be determined which or whether one drug was the sole and direct cause of the death. In drug induced deaths with opioids present, blood levels cannot be used to determine the cause of death because the level of tolerance cannot be determined, pulmonary edema should be present and when multiple drugs are involved, the cause of death cannot be attributed to any particular substance.

Currently, much of the information regarding abuse of prescription drugs, including OxyContin, is anecdotal. Anecdotal information should not dictate policy, but be used to determine when additional studies need to be done to gain further understanding of the problem, and to assist in the development of solutions. One method of doing this is the development and implementation of post-marketing surveillance programs like the program for tramadol described above. Programs of this type should have the ability to proactively gather information on the abuse and diversion of prescription drugs over a broad geographic distribution in a timely fashion. By looking at the data in the context of both national and local legitimate patient exposure to the drug, rates of abuse can be developed that would enable comparisons across drugs, and provide on context in which the abuse may be occurring.

The data collected should be analyzed to establish the need for more in depth studies to determine the nature and scope of the problem in a specific area. From this information, interventions can be developed and evaluated that are specific to the problems in that area. As described in the tramadol study, evidence of abuse of prescription drugs is often localized making local remedies more applicable than national approaches that can be helpful in one area and detrimental in another.

SUMMARY

Abuse of prescription drugs is not a new problem and has resulted in the passage of numerous laws over the past century. These laws have restricted the availability of certain medications that have demonstrated abuse liability. The effect of these laws on the availability of controlled medications to patients is unknown. Periodically, the media has covered the problems of prescription drug abuse extensively, often focusing on one particular drug. This intense reporting on that drug may have a deleterious effect of increasing interest in that drug in the drug abusing community and therefore, increasing the problem. The anecdotal reports in the media are not based on sound scientific information, but may be used to develop policy. Ongoing studies of prescription drug abuse and diversion must be developed that have clear objectives and are based on the best techniques currently available. Policy decisions should be based on scientific information using multiple sources of information. As described by Jenkins (1999), "…the degree of panic associated with a social problem depends upon the wider cultural and political context rather than on any intrinsic qualities of the phenomenon itself."

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THE DEA PERSPECTIVE ON PRESCRIPTION DRUG DIVERSION AND ABUSE

F. Sapienza

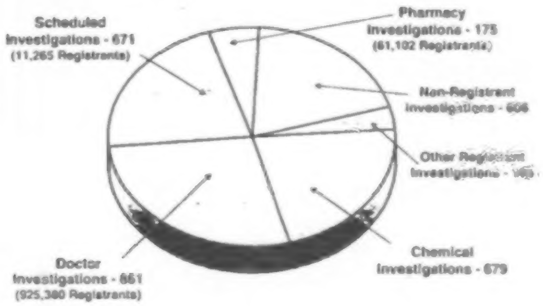
The diversion and abuse of controlled prescription drugs is one of the major reasons for enactment of international drug control treaties and domestic laws. The Controlled Substances Act of 1970 (CSA) mandates the Drug Enforcement Administration (DEA) to prevent, detect and investigate the diversion of legally manufactured controlled substances while ensuring an adequate supply to meet legitimate needs. The demand for prescription controlled substances is manifested through diversion or when efforts to prevent diversion are effective, through illicit production, e.g. amphetamine and methamphetamine. DEA experience indicates that although prescription drug diversion and abuse are difficult to measure, they can be identified for most controlled substances in some areas. Failure to deter diversion and abuse adversely impacts the public health through the direct health consequences of abuse of the substances or indirectly through the imposition of more stringent controls on useful medicines. Prevention of diversion and abuse is the responsibility of all facets of the health care community, industry, and governments.

The CSA mandates a closed system of distribution for all handlers of controlled substances. This is accomplished through a series of controls beginning with the registration of all handlers of controlled substances and includes record keeping, reporting, security, manufacturing, import and export controls. There are civil fines, and administrative and criminal penalties for CSA violations. The CSA provides for minimum legal standards for handling controlled substances. DEA registrants are expected to comply with the "spirit" of the CSA.

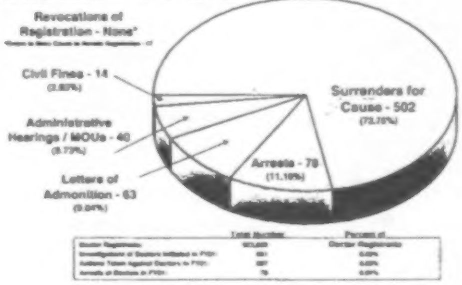
Despite these controls, diversion occurs, primarily at the retail level (practitioners and pharmacies) through illegal distribution, inappropriate prescribing or filling of prescriptions, doctor shopping, and forged prescriptions. Thefts at all levels of the distribution chain, illegal importation and Internet sales are also sources of diversion. There are currently over one million DEA registrants, the majority at the retail level.

Approximately 400 specialized DEA Diversion Investigators are responsible for inspecting the registrant population, primarily at the manufacturer level, and investigating diversion. The charts below show the percentages of various DEA investigations. These represent approximately 0.01% of the registered practitioner population. Investigations are initiated by information from state/local authorities (who conduct most diversion investigations), medical boards, confidential informants, patients, and pharmacists. DEA does not investigate practitioners without cause.

Total DEA Diversion Investigations for FY 2001 - 3,097



DEA Diversion Investigations of Doctors - FY 2001

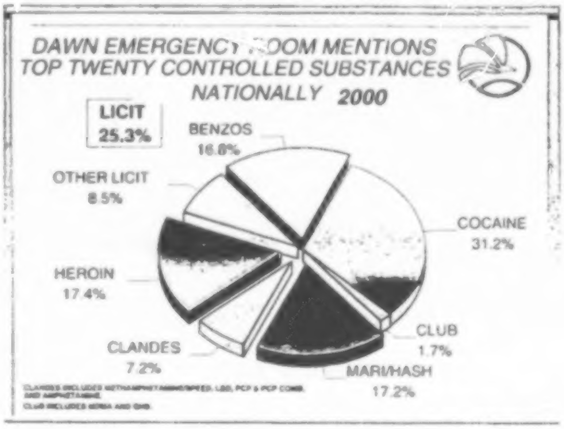


Most Commonly Diverted and Abused Pharmaceuticals

Although all drug abuse indicator systems are imprecise, together they show that the diversion and abuse of prescription controlled substances are significant problems. This is particularly true for narcotic analgesics and to a lesser degree, sedative-hypnotics (e.g., benzodiazepines). DEA, as an agency responsible for protecting the public health and safety must often make decisions before results from scientifically designed and controlled studies are available. Because of this, anecdotal evidence plays an important role in alerting agencies to potential and actual problems and the need for quick action. This information is then compared to and corroborated with other more scientifically derived information.

DEA's 25 domestic field offices file quarterly reports on the most commonly diverted and abused controlled substances. For the first quarter of 2002, the narcotic analgesics hycrocodone, oxycodone (increasingly OxyContin) and methadone and the benzodiazepines (alprazolam and diazepam) are the most frequently reported diverted controlled substances. Hydrocodone products were reported by all 25 domestic divisions. DEA is reviewing a petition to reschedule hydrocodone combination products from Schedule III to Schedule II. Schedule III codeine products, morphine and meperidine were also mentioned by a number of DEA field offices. The stimulant, methylphenidate and the dissociative anesthetic, ketamine were reported by more than five divisions. Carisoprodol and tramadol are the most commonly reported non-controlled substances. These reports show the regional variability of prescription drug abuse and diversion.

The Drug Abuse Warning Network (DAWN) data for 2000 shows that licit pharmaceutical controlled substances account for over 25% of the emergency room mentions for all controlled substances. This is second only to cocaine and greater than heroin, marijuana and other illicitly produced substances. The benzodiazepines (alprazolam, clonazepam, lorazepam and diazepam) and narcotic analgesics (oxycodone, hydrocodone and methadone) are involved in the majority of these mentions.

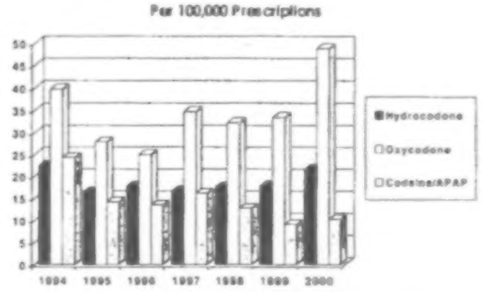


Since 1997, the DEA has been developing a data system that collects information on analyzed drug evidence submitted to nonfederal forensic laboratories. There are about 300 such laboratories that handle more than 1.3 million cases in which drug evidence is chemically verified. The National Forensic Laboratory Information System (NFLIS) currently captures about 70% of these analyses. Each piece of evidence is chemically verified. The following tables depicting NFLIS data (2001) show a good correlation with that from DAWN ED mentions and DEA field office reports.

Description	Total	%
CANNABIS	275,791	36.15
COCAINE	234,890	30.79
METHAMPHETAMINE	100,626	13.19
HEROIN	47,844	6.27
MDMA	8,526	1.12
ALPRAZOLAM	6,857	0.90
NON-CONTROLLED NON-NARCOTIC	6,592	0.86
HYDROCODONE	5,569	0.73
OXYCODONE	4,792	0.63
PSEUDOEPHEDRINE	3,391	0.44
DIAZEPAM	3,357	0.44
PHENCYCLIDINE	2,272	0.30
CLONAZEPAM	2,012	0.26

Hydrocodone and oxycodone account for approximately 70% of the analgesic drugs reported by NFLIS while alprazolam and diazepam account for more the 75% of the benzodiazepines. DEA laboratory analyses show that hydrocodone and oxycodone accounted for about 80% of the analgesics identified (STRIDE data).

DEA has engaged in a data collection effort to identify the scope, magnitude and severity of the diversion and abuse of OxyContin (time-release oxycodone product). All data point to a serious problem with the diversion and abuse of oxycodone, and where information is available, to a very serious problem with OxyContin. An informal survey of drug abuse treatment providers indicate that some centers report as great as 90% of treatment admissions in 2000 and 2001 in portions of some states attributed to OxyContin. An examination of theft data for controlled substances reported to DEA shows that oxycodone thefts involving armed robberies occur more than four times more frequently than those involving the next most frequently encountered substance.


DAWN Emergency Department Mentions

An examination of DAWN emergency department mentions shows that although there are more hydrocodone mentions annually than for oxycodone, when one considers these mentions per 100,000 prescriptions dispensed, oxycodone mentions are much higher.

An examination of the geographic distribution patterns for oxycodone and OxyContin shows a wide variability from state to state. Those states having a more serious problem with oxycodone have the highest levels of distribution. It also appears that those states with the lowest levels of distribution and prescription of oxycodone have some form of prescription monitoring system and are not reporting problems with oxycodone. Prescription monitoring systems are an effective means of preventing and identifying diversion.

Factors Effecting Diversion

There are a number of factors that affect the level (not necessarily the rate) of abuse of controlled substances. These include the following: 1) the nature of the substance/product; 2) availability; 3) promotional/marketing activities; 4) prescribing/dispensing practices; 5) informational/educational efforts; and 6) law enforcement/regulatory actions. Of particularly current concern to DEA are the marketing and promotional activities of some companies that we believe is contributing to the excess availability, over prescribing and ultimately abuse and diversion. Direct-to-consumer advertising of controlled substances, although not expressly prohibited by the CSA, is inconsistent with the spirit of the CSA. The US is one of two countries that allow such practices which are condemned by the International Narcotics Control Board as contrary to the 1971 Convention and WHO Guidelines on ethical promotion and advertising practices. Four of the six top brand name controlled products have been or currently are advertised directly to the consumer; these include Schedule II controlled substances intended for the treatment of children. The DEA has unsuccessfully asked the regulated industry for voluntary cooperation and will issue a policy statement in the very near future.

CONCLUSION

DEA's goal is to impact and prevent the diversion and abuse of legitimately manufactured controlled substances without impacting the legitimate use of these substances. This can only be accomplished with the full cooperation of the medical community, the regulated industry and state and local authorities.

SYMPOSIUM IX

COCAINE ADDICTION: TO THE AMYGDALA AND BEYOND

K. M. Kantak and F. Weiss, Chairpersons

Cocaine addiction is a chronically relapsing brain disease, but its neurobiological basis is not yet well understood. Although the nucleus accumbens is viewed as a critical target for mediating cocaine reward, addiction is a complex process, and to understand it fully, one must reach beyond this structure. Many pre-clinical studies to date have explored the role of the basolateral amygdala and its associated neural and cognitive functions in regulating certain aspects of the cocaine addiction process. However, recent brain imaging studies show that craving induced by exposure to either cocaine-associated cues or a priming injection of cocaine produce specific changes in the pattern of activation not only in the amygdala, but also in the anterior cingulate, basal ganglia, prefrontal cortex, hippocampus and cerebellum of abstinent cocaine addicts. Thus, to gain insight into basic brain mechanisms underlying cocaine addiction, one must explore even beyond the amygdala. In this symposium, speakers highlighted their past research concerning the nucleus accumbens and amygdala as well as detailed their current research concerning involvement of other neurobiological systems (*e.g.* cortex, hippocampus and dorsal striatum) in regulating different aspects of the cocaine addiction process. Using cocaine self-administration methods, four pre-clinical perspectives were presented and the findings discussed by Dr. Charles O'Brien in terms of the insights they may provide for understanding the basic brain mechanisms underlying human cocaine addiction.

NEUROCOGNITIVE MECHANISMS REGULATING COCAINE-SEEKING BEHAVIOR STUDIED IN A DRUG MAINTENANCE/CUE REINSTATEMENT MODEL

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SUMMARY

In laboratory animals, response-contingent conditioned stimulus cues that are associated with cocaine self-administration induce what is termed drug-seeking behavior (i.e., responding maintained by drug-associated cues at times when drug is not immediately available; Goldberg *et al.*, 1981). Conditioned stimuli receive their salience via basolateral amygdala-dependant conditioned stimulus-reward learning mechanisms (Whitelaw *et al.*, 1996; Meil and See, 1997; Grim and See, 2000; Weiss *et al.*, 2000). Earlier lesion studies demonstrated that conditioned stimulus-reward learning is dependent on an intact basolateral amygdala (Cador *et al.*, 1989; Everitt *et al.*, 1991). Recently, we reported that lidocaine-induced inactivation of the rostral and caudal basolateral amygdala (BLA) produced dissociable effects on disrupting cognitive performance (Kantak *et al.*, 2001) and on disrupting drug-seeking behavior studied in a drug maintenance/cue reinstatement model (Kantak *et al.*, 2002a). This model used a second-order schedule of cocaine delivery coupled with response-independent contextual stimuli and response-contingent conditioned stimuli. Drug-taking behavior was not affected. The findings extended earlier studies by suggesting a functional heterogeneity between the rostral BLA and caudal BLA for processing associative aspects of drug-seeking behavior under different testing conditions and that the BLA does not play a role in regulating drug-taking behavior.

Stimulus-response learning, on the other hand, has been shown to be dependent on lateral dorsal striatal function (Kantak *et al.*, 2001). A role for the lateral dorsal striatum (DST) and its associative functions in regulating cocaine self-administration behavior is not clear because there is little published work in this area. Interestingly, human brain imaging studies demonstrate that cocaine injection in abstinent addicts produces activation in the caudate nucleus (Breiter *et al.*,1997, whereas presentation of cocaine-paired cues alone does not (Grant *et al.*, 1996). The degree of activation correlated with "rush" ratings, but not "craving" ratings. The possible importance for lateral dorsal striatal function in regulating some aspect of cocaine addiction is also implicated in studies showing that while dorsal striatal microinjection of the D2 receptor antagonist spiroperidol had no effect (Phillips *et al.*,1983), microinjection of the D1 receptor antagonist SCH 23390 increased responding maintained under an FR schedule of cocaine delivery (Caine *et al.*,1995). Under a second-order schedule of cocaine delivery in well-trained rats, dopamine levels in the dorsal striatum were shown to increase only toward the end of the initial 20-min drug-free interval and to continue to increase after subsequent intervals when cocaine was available (Ito *et al.*, 2002). It was suggested that the dorsal striatum might somehow be involved in regulating drug-seeking behavior. Using our maintenance/reinstatement model of cocaine self-administration, experimental findings suggested that stimulus-response functions of the lateral DST may regulate the dose-related effects of self-administered cocaine because the lidocaine-induced changes in behavior during the maintenance and cocaine primed reinstatement tests resembled the effects of exposure to increasingly lower doses of cocaine, respectively (Kantak *et al.*, 2002b). Given the lack of an effect of lidocaine during reinstatement tests where drug-paired cues were presented alone, the lateral DST did not appear to regulate drug-seeking behavior per se (i.e., responding maintained by drug-associated cues at times when drug is not immediately available).

Mounting evidence indicates an important role for the prefrontal cortex in regulating certain aspects of cocaine self-administration behavior. An early study conducted by Goeders and Smith (1983) demonstrated that rats will self-administer cocaine directly into the medial PFC and a recent study by Park *et al.*, (2002) demonstrated that a priming injection of cocaine directly into the medial PFC will also reinstate extinguished drug-seeking behavior previously maintained under a second-order schedule of cocaine delivery. Thus, increases in dopamine neurotransmission in the medial PFC may be necessary for cocaine and cocaine-paired stimuli to initiate responding. It was at first surprising, then, that Weissenborn *et al.*, (1997) showed that excitotoxic lesions of the medial PFC facilitated acquisition of cocaine self-administration. However, lesioned rats had higher response rates overall compared to the control, and after acquisition was complete and the rats were placed on a second-order schedule of drug delivery, the same lesions altered the pattern of drug-seeking behavior during the first drug-free interval without altering the amount of responding. Specifically, the index of curvature [a measure indicative of the degree of scalloping within the cumulative record that is characteristic of fixed-interval based schedules of cocaine delivery] was smaller in lesioned rats compared to the control, suggesting a deficit in behavioral inhibition (prefrontal cortex-dependent function) that led to faster acquisition and a more linear (non-scalloped) or continuous rate of responding. Because lesioned rats showed other signs of behavioral disinhibition, it is likely that lesions of the medial PFC interfered with the ability of cocaine-paired stimuli to regulate the temporal pattern of second-order responding. Similar to these findings, lidocaine-induced inactivation of the lateral PFC caused a disruption in the scalloped response pattern seen during cocaine self-administration maintained by our second-order schedule of cocaine delivery (Black *et al.*, 2002). The persistence of a linear pattern of responding may be related to the inability of PFC inactivated rats to switch behavioral strategies over a delay when required to do so in associative tasks guided by external sensory stimuli (Di Pietro *et al.*, 2002).

Various studies showing changes in drug-seeking and drug-taking behavior after manipulation of the hippocampus suggest that the environmental context of the cocaine experience may also help regulate these behaviors through hippocampally-dependant processes (stimulus-stimulus associations or contextual learning). In our studies examining the role of the hippocampus in regulating addiction-related behavior, lidocaine inactivation of the dorsal SUB, but not ventral SUB, significantly decreased drug-taking behavior as well as drug-seeking behavior during the maintenance phase when cocaine was made repeatedly available with both contextual and conditioned stimuli. During the reinstatement phases, inactivation of the dorsal SUB did not alter drug-seeking behavior induced by presentation of cues alone or by cues presented in combination with a priming injection of cocaine. Others have shown that electrical stimulation of the ventral SUB reinstates drug-seeking behavior examined after a period of extinction from cocaine self-administration (Vorel *et al.*, 2001), which is consistent with studies showing that inactivation of the ventral SUB selectively reduces drug-associated stimulus-maintained responding (Hitchcott and Phillips, 1997). In comparison, inactivation of the ventral SUB does not influence behavior maintained solely by a primary reward (Burns *et al.*, 1993), which may explain the lack of an effect of ventral or dorsal SUB lesions on responding maintained by cocaine alone (Caine *et al.*, 2001). As inactivation of the ventral SUB and dorsal SUB disrupts cognitive behavior guided by contextual stimuli rather than by conditioned stimuli (Black *et al.*, submitted), it appears that the ventral SUB and dorsal SUB may have dissociable roles in regulating drug-seeking and drug-taking behavior, but only when discriminable contextual stimuli predictive of drug availability are present (Weiss *et al.*, 2001).

Based on a second-order schedule of drug delivery, we generated the following working hypothesis using available data to date. After a rat enters an environment where drug is known to be available, the entorhinal cortex representation of this context activates the hippocampus, which strengthens the associations among drug-paired contextual stimuli (sound, test chamber, drug craving?). This process enables contextual cue-induced drug-seeking (ventral SUB?) and drug-taking (dorsal SUB?) behavior. During the first 15-20 min in a drug-paired environment, experienced rats behave as if they are unaware of the temporal location of drug. The cumulative response records showing continuous linear responding support this view, which suggests that initially rats search for drug in a retrospective manner. This may be due to an initial inhibitory influence of cocaine (via increases in DA in the PFC) on the prefrontal cortex (medial? lateral?). When the prefrontal cortex becomes disinhibited through feedback mechanisms that are activated by continued cocaine use (causing reduction in DA in the PFC), rats revert to a prospective drug search strategy, as they appear to use previously acquired information about the temporal location of drug (scalloped pattern in the cumulative response records) after the first 15-20 min.

Concurrently, after the initial intake of cocaine, the mesolimbic dopamine pathway (reward) and the nigrostriatal dopamine pathway (motor) are activated. When the dorsal striatum (lateral?) is activated by cocaine, this structure is primed to strengthen the association between relevant sensory stimuli (via sensory input from the sensorimotor cortex) and motor responding that leads to reward. The information concerning the strength of this association indirectly reaches the nucleus accumbens (core?), which utilizes this information to establish reward value of a particular dose of cocaine. Simultaneously, cues that are discretely present at the time of cocaine delivery activate the BLA (caudal?) via cortical sensory input from temporal area 3. Associative processes of the caudal BLA strengthen the relationship between this class of stimuli (CS) and cocaine reward, the information of which reaches the caudal BLA by way of the nucleus accumbens (shell?). This conditioned associative information, along with contextual associative information from the hippocampus, feeds back to the nucleus accumbens to promote further drug-seeking and drug-taking behavior. Input from the now activated prefrontal cortex ensures that this occurs in a temporally specific manner. After abstinence, the BLA (rostral?) and hippocampus (ventral SUB?) circuits are primed through repeated conditioning to maintain drug-seeking behavior in the absence of drug reward, when dopaminergic tone is relatively low. If the prefrontal cortex (medial? lateral?) is chronically dysregulated with chronic cocaine use (inhibition of the normal feedback mechanisms that activate the PFC), then binge-like behavior may ensue because the cues that control recreational patterns of cocaine use are ignored. Further investigation of these learning circuits in regulating addiction-related behavior is in progress.

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NEUROPHARMACOLOGICAL SUBSTRATES OF COCAINE-SEEKING INDUCED BY DRUG-RELATED CONTEXTUAL STIMULI.

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SUMMARY

The conditioning of the pharmacological actions of drugs of abuse with discrete environmental stimuli has been implicated as a major factor in the abuse potential of these substances. Drug-related stimuli can evoke drug craving that may result in resumption of drug-taking in abstinent individuals (O'Brien *et al.*, 1998) or elicit automatic responses that lead to drug-seeking and relapse without the intervention of distinct feelings of craving (Miller and Gold, 1994; Tiffany and Carter, 1998). Learned responses to drug-related stimuli have, in fact, been proposed to be among the most important factors responsible for the high rates of relapse associated with drug addiction (O'Brien *et al.*, 1998; O'Brien and McLellan, 1996; Leshner, 1997).

Effective behavioral procedures have become available in recent years to model this aspect of the addictive cycle in rats. Data from operant response-reinstatement models implemented to investigate drug-seeking behavior associated

with exposure to drug-related environmental cues in rats, indicate that drug-predictive discriminative stimuli (SD) have remarkably potent effects on subsequent cocaine-seeking behavior, in that their effects are highly resistant to extinction and persist over long periods of abstinence. Specifically, exposure to a cocaine SD, but not an SD associated with non-reward (saline), produced robust recovery of operant responding following extinction that remained unaltered throughout a 35 day period of reinstatement testing (Weiss et al, 2001). Strikingly, responding elicited by this stimulus was still observed after 4 months of abstinence at levels similar to those maintained earlier by cocaine (Ciccocioppo *et al.*, 2001; Weiss et al, 2001).

Neurochemical, neuroanatomical, and pharmacological investigations implicate dopamine-rich forebrain regions including the basolateral amygdala (BLA) and prefrontal cortical regions in the mediation of the motivating effects of cocaine-related environmental stimuli (Ciccocioppo *et al.*, 2001; Weiss et al, 2001; Weiss, *et al.*, 2000). Exposure to a cocaine SD elevated extracellular dopamine levels in the BLA and selectively increased Fos immunoreactivity in the same brain region as well as in the Cg1/Cg3 regions of the prefrontal cortex (anterior cingulate and prelimbic cortex) (Weiss et al, 2001; Weiss, *et al.*, 2000). Both conditioned reinstatement and Fos protein expression induced by the cocaine SD were reversed by pretreatment with the selective dopamine D1 receptor antagonists SCH 39166 and SCH 23390, findings that implicate D1-dependent neural mechanisms within the BLA and prefrontal cortical regions in conditioned reinstatement elicited by cocaine-predictive environmental stimuli. Moreover, the effects of the cocaine SD on reinstatement and Fos expression as well as the reversal of these effects by D1 antagonists was identical in rats tested after short-term (3weeks) or long-term (4 months) abstinence (Ciccocioppo *et al.*, 2001; Weiss et al, 2001). This observation suggests that the repeated pairing of cocaine with drug-predictive stimulus may have resulted in some long-lasting neural plasticity within the BLA and medial prefrontal cortical regions by which sensitivity to these stimuli is maintained.

Overall, the results confirm that the efficacy of cocaine-predictive discriminative stimuli to elicit drug-seeking behavior remains intact over prolonged periods of abstinence and, by extension, support the hypothesis that learned responses to drug-related stimuli are an important factor in compulsive drug-seeking behavior and long-lasting vulnerability to relapse. Moreover, the data implicate the basolateral amygdala as well as Cg1/Cg3 regions of the prefrontal cortex as candidate sites for the mediation of cue-induced cocaine-seeking behavior, and suggest that the D1 receptor may represent an important neuropharmacological substrate for conditioned reinstatement associated with cocaine-related contextual stimuli.

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NEUROCHEMICAL EVIDENCE THAT LIMBIC AND CORTICAL BRAIN REGIONS ARE INVOLVED IN COCAINE-SEEKING BEHAVIOR

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SUMMARY

Expression of Fos protein, the product of the immediate early gene c-fos, was used as a neurochemical marker to examine neuronal activation associated with incentive motivational effects of cocaine priming and cocaine-associated stimuli. The incentive motivational effects of these stimuli were assessed by measuring cocaine-seeking behavior, operationally defined as lever presses in the absence of cocaine reinforcement on a lever previously associated with cocaine reinforcement. This behavior demonstrates the degree to which an animal is willing to work for cocaine when cocaine is withheld, and therefore, is thought to provide an index of motivation. Rats were either trained to press a lever to receive IV cocaine infusions on a VR5 schedule of reinforcement or they received yoked saline infusions (Control). They then received 21 daily exposures to either the self-administration environment (Extinction) or a different environment (No Extinction) without cocaine available in either environment. Extinction training was employed to decrease incentive motivation for cocaine elicited by the self-administration environment. Animals were then tested for cocaine-seeking behavior after exposure to the cocaine self-administration environment, and some animals were further tested for reinstatement of extinguished cocaine-seeking behavior by saline and cocaine priming injections. The animals were sacrificed 90 min after testing was complete, a time at which Fos protein expression is maximal after stimulus exposure.

As expected, the No Extinction group exhibited significantly more cocaine-seeking behavior than the Control and Extinction groups after exposure to the self-administration environment, whereas both cocaine-experienced groups (Extinction and No Extinction) exhibited an increase in cocaine-seeking behavior relative to the Control group after priming. Exposure to the self-administration environment also produced conditioned Fos expression, evident as an increase in the No Extinction group relative to Control and Extinction groups, in the anterior cingulate cortex, basolateral amygdala, hippocampal CA1 region, dentate gyrus, and nucleus accumbens shell regardless of whether priming injections were given. Furthermore, these changes were also observed in a No Extinction group tested without the lever present, suggesting the increases in Fos protein in these regions are not simply due to an increase in lever pressing per se, but are likely due to incentive motivational effects of the environment. A distinctly different pattern of Fos protein expression was observed after the priming injections, in which Fos was enhanced in the ventral tegmental area, caudate-putamen, substantia nigra pars reticulata, entorhinal cortex, central amygdala, lateral amygdala, arcuate nucleus, and central gray area regardless of conditioning group. These changes likely reflect an unconditioned effect of either cocaine or injection stress since they were observed in saline-yoked controls given cocaine for the first time. The priming injections also enhanced Fos expression in the anterior cingulate cortex, but only in cocaine-experienced groups, suggesting this enhancement is likely due to incentive motivational effects produced by cocaine priming. The results suggest that different corticolimbic circuits are activated by cocaine-paired environmental stimuli versus priming injections, and that the anterior cingulate cortex may be part of a common pathway activated by both types of stimuli (Neisewander *et al.*, 2000).

Subsequent experiments investigated the role of the amygdala in cocaine-seeking behavior after exposure to a self-administration environment, as well as its role in acquisition and expression of cocaine-conditioned place preference (CPP). Animals that had been trained to self-administer cocaine received either excitotoxic lesions of the basolateral complex of amygdaloid nuclei (BLC; includes lateral and basolateral nuclei) or sham surgery. After recovery from surgery, the animals were tested repeatedly for cocaine-seeking behavior. Lesion animals exhibited more cocaine-seeking behavior and shorter response latencies relative to sham controls across tests, suggesting the lesion increased resistance to extinction of cocaine-seeking behavior. The animals then underwent a 2-day place conditioning procedure, in which cocaine was paired with confinement to a distinct environment on one day and saline was paired with a distinct environment on the other day, counterbalanced for order. During conditioning, animals form an association between the rewarding effects of cocaine and the cocaine-paired environment, such that the environment acquires incentive motivational effects that are reflected on the test day as an increase in the amount of time spent in the cocaine-paired environment relative to the saline-paired environment. In contrast to sham animals, lesion animals failed to acquire cocaine-CPP. In a subsequent experiment, animals underwent place conditioning and then received BLC lesions or sham surgery in order to assess lesion effects on expression and extinction of an established cocaine-CPP. The lesions failed to alter expression of cocaine-CPP, but increased resistance to extinction of cocaine-CPP across repeated test days (Fuchs *et al.*, 2002). Finally, the ability of either cocaine or amphetamine infused directly into the basolateral (BlA) or central (CeA) amygdaloid nuclei to produce CPP was examined. Only infusions into the CeA produced CPP, suggesting that the CeA, but not the BlA, is capable of initiating rewarding effects of psychomotor stimulants (O'Dell *et al.*, 1999). However, the finding that BLC lesions impair acquisition of cocaine-CPP suggests that the BLC may be involved in assigning incentive value to the initially neutral environmental stimuli, a process essential for forming an association between those stimuli and the rewarding effects of cocaine. Furthermore, the finding that BLC lesions increase resistance to extinction of cocaine-seeking behavior and cocaine-CPP suggests that the BLC may be involved in modifying existing representations of the incentive value of cocaine-paired stimuli, which normally occurs during extinction (i.e., the stimuli are devalued during extinction since they are no longer predictive of cocaine).

The BlA is interconnected with regions of the prefrontal cortex, including the prelimbic (PrL) subregion. A final experiment was conducted to examine the role of the prelimbic (PrL) subregion of prefrontal cortex in acquisition, extinction, and cocaine-primed reinstatement of cocaine-CPP. Pre-conditioning, excitotoxic lesions of the PrL failed to alter acquisition or extinction of cocaine-CPP, but attenuated cocaine-primed reinstatement of extinguished cocaine-CPP. The latter finding suggests that the PrL is involved in processing the incentive motivational effects of cocaine priming injections. Although we failed to find evidence for a role of the PrL in the incentive motivational effects of cocaine-paired stimuli, previous research has shown that this region is activated by exposure to a contextual, cocaine discriminative stimulus (Ciccocioppo *et al.*, 2001) and is involved in acquisition and expression of cocaine-CPP (Tzschentke and Schmidt, 1998). Collectively, the findings suggest that the PrL may be involved in the incentive motivational effects of cocaine priming and cocaine-associated stimuli; however, its role may be nonessential and compensated by other parallel systems.

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NEUROPHYSIOLOGY OF MESOLIMBIC SYSTEM DURING SELF ADMINISTRATION OF COCAINE

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SUMMARY

One goal of the neurophysiology of substance abuse is to clarify the neural signals in the mesolimbic system that mediate the behaviors to obtain cocaine. This mode of research is based on the view that an initial drug experience induced by cocaine's actions on its pharmacological targets induces a long-lasting action within the CNS that favors repeated behavior to obtain additional drug. The primary pharmacological and secondary sensory, cognitive or emotional effects of cocaine are presumed to induce persistent changes that enable behavioral activation at a later time. Interconnected zones of the mesolimbic system, including the medial and lateral prefrontal cortex, amygdala, nucleus accumbens, DA and non DA neurons of the VTA are postulated to process an initial 'reward signal', store

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information in a persistent mode and thus allow later cues and conditions to evoke the cocaine seeking behavior. The task of neurophysiology is to determine where and when neuronal signals appear within this system to mediate behaviors specifically directed toward drug seeking.

An initial hypothesis at the start of this investigation a decade ago was that a neural signals in the form of elevated or depressed activity should appear at the time after an injection of cocaine induced 'reward' as a consequence of an enhanced action of dopamine, a postulated 'reward substance'. The initiation of such work was greatly facilitated by the advent of enhanced micro electronics for multi channel recording and methods for use of chronically implanted recording micro wires, as developed in this laboratory. Initial studies employed use of a single dose of 1 mg/kg cocaine injected I.V. on an FR1, FR5, or FR10 schedules. This protocol normally resulted in regular responding with a lever press to obtain single doses at intervals of three to five minutes.
Neurons in both the nucleus accumbens and the medial prefrontal cortex exhibited similar patterns of responding in this paradigm. Fifty percent of neurons showed no alteration of activity either before or after the lever press. About ten percent of neurons in these regions responded with a short period of elevated or depressed activity a few second prior to the lever press. A subgroup of other neurons revealed changes in activity after the lever press, during and after the ten second period of cocaine infusion. The changes in activity often decayed gradually during the three-four minute inter trial interval as though paralleling the action of the drug and resumption of lever pressing when the drug action became minimal. Further detailed study of video records indicated that the excitatory responses preceding the lever press were often correlated with the onset or termination of a component of the movement sequence (turning, arm raising, head movement) leading up the to the lever press. Also, movement of the limbs, turning or raising the head in contexts other than those directed toward lever press for cocaine did not evoke neuronal responses.

Thus there appears to be a 'reward-specificity' in that activity correlated with movement, but only in the context of drug seeking. It became clear that neuronal activity in the mesolimbic system does not support a simple mode reflecting the time-envelop of a postulated reward function. The neuronal responses in mesolimbic system appeared to reflect the activation of circuits designed to generate specific drug seeking behaviors. It is important to note that this occurred at the end of a trial when the blood levels would be expected to be minimal. Indeed, the direct effect of cocaine infusion appears to yield a period of suppression of behavior during which the rat enters a period of stereotypic behavior with head movements and chewing. When the drug action wears off the rat resumes cocaine seeking behavior, and neuron responses appear that correlate with activation of behavioral sequences.. We conclude that the neuronal events evoked by pharmacology of cocaine, here contributing to a period of suppression of activity, are quite different from the discrete patterns that correlate with the activation of drug seeking behavior.

Further studies of these phenomena compared the neuronal responses correlated with similar lever presses to obtain cocaine versus heroin. In this case the rat was trained to press a level for cocaine for the initial half of a session and then switch to heroin, or visa versa, at the end of the session. In these cases it appeared that similar patterns of activity were presented around the time of lever press, but for the most part, different groups of neurons became active specific to the drug seeking behavior. We postulate that the anticipation of reward for the future generates activity within specific subsets of neurons, which in turn may have the capability to initiate quite similar patterns of behavior to achieve lever pressing and resulting drug reward.

A new hypothesis is that each reward goal may generate its own neuronal pattern of anticipatory representation.

It is often asked how the traditional analysis of drug dose-response relates to this form of neurophysiological analysis. Our view is that most of the prominent responses so far studied are encountered at the end of a time interval between repeated self dosing. This is when drug levels have fallen to a minimal dose. Within the range studied, increasing a dose primarily prolongs the time before the next lever press, while lowering the dose shortens the time. It is as though the neural events that precipitate the behavioral activation may require that a relatively constant low blood level of drug be attained. Out view is that the neural events are not likely to be a result of direct drug action but instead a result of frontal cortical process of conditioned cues and interactions with resident memories. This concept may apply in studies discussed of drug seeking at the start of a self-administration session (Kantak, this volume). These mechanisms are several steps removed from simple dose response relations and provide the neural basis of phenomena revealed drug relapse behavior many days (Weiss, this volume) after drug is no longer in the blood.

Initial recording of presumed dopamine neurons include those in the ventral tegmental area that exhibited long duration spikes of 2-3 msec and were inhibited by apomorphine. These putative DA neurons were found to respond at the time of operant responses, or to conditioned tone cues during behavioral events prior to sucrose or ethanol/sucrose reward. Subsets of neurons revealed inhibition when an unanticipated reward was encountered. These early findings indicate that phasic activity of dopamine neurons may be related more to the anticipation of events leading to reward.

The circuits in the frontal cortex critical for drug seeking certainly mediate many other functions. Additional studies of a spatial delayed match/nonmatch to sample task reveal that medial frontal cortex and nucleus accumbens codes information related to space (position of the levers), task (sample versus match phase), and performance (correct versus error). These studies indicate that processing in the drug seeking regions also plays a role in formulation future behavior in relation to short and long term memory. Other studies of lateral prefrontal cortex indicate that ongoing assessment of taste cues regulate choices of behavioral options

The hypothesis emerging from this early analysis is that the immediate effect of cocaine reward may be to induce a transient sensory or cognitive influence that persists largely as a memory. This primary effect probably occurs in parallel with long duration cell biological influence of a different nature, perhaps related to a sensitization of synaptic mechanisms. The postulated persisting memory of drug experience would contribute to the process of interpreting environment and internal cues and generating anticipatory activity specific to the future drug reward. It should be noted that the persistent effect should reside in the CNS as a distributed pattern of altered synaptic strengths and thresholds for activating excitation or inhibition. Neural activity patterns will be observed only when specific neural events probe these longer lasting functional and structural changes.

Neural representations generated within the frontal cortex and mesolimbic system are hypothesized to have the intrinsic ability to trigger specific targeted behavioral sequences. The future study of this newly formulated hypothesis will require the study of the elaboration of the spatial and temporal organization of mesolimbic patterns of activity within ensembles of neurons in the mesolimbic system that represent specific reward to be attained by future behavior.

SYMPOSIUM X

LONGITUDINAL STUDIES OF PATHWAYS TO DRUG ABUSE: CURRENT STATUS, EMERGING FINDINGS, AND IMPLICATIONS FOR PREVENTION

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Longitudinal studies are valued for their ability to investigate temporal sequences of events and to explore the contributions of an individual's characteristics at one point to subsequent points. As important as this is, longitudinal studies also provide an additional heuristic benefit. Cross-sectional research assesses characteristics and their relationships at a single point. This promotes a static view of risk and protective factors as well as outcomes. In contrast, longitudinal studies support interactive and developmental concepts and models. While both cross-sectional and longitudinal research identify risk and protective factors, longitudinal research is more likely to nest them in a perspective of patterns and pathways that accurately depicts the progression of behavior.

In the field of research on drug abuse etiology, there are a number of long-term longitudinal studies that follow cohorts of children and adolescents into young adulthood and beyond in order to trace the developmental course of substance abuse and identify key risk and protective factors associated with onset of use and progression to dependence and addiction. Several of the best designed and most comprehensive of these studies are at point where they have followed their subjects for a sufficient time and number of assessment waves to provide new and very powerful information about the onset and development of substance abuse problems. This symposium brought together investigators on a five of these studies to present their findings, discuss their current status, identify emerging trends across studies, and highlight implications for prevention. Papers were presented by Drs. Laurie Chassin, Ralph Tarter, Thomas Wills, and Rolf Loeber, and Dr. Robert Pandina served as discussant.

DRUG ABUSE RISK IN CHILDREN OF ALCOHOLICS: MEDIATING AND MODERATING MECHANISMS

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Although parent alcoholism is a robust risk factor for drug disorders, less is known about the mechanisms that mediate or moderate that risk. Knowledge of such mediating and moderating factors both advances knowledge of the etiology of drug disorders and suggests directions for preventive intervention with high-risk groups.

Sher (1991) proposed three inter-related mediating pathways. (children of alcoholics (COAs) are thought to experience greater pharmacological benefits from using drugs (the substance use effects pathway) as well as more stress and negative affect, which motivate their drug use (the stress and negative affect pathway). The third mechanism is the behavioral undercontrol pathway. According to this mechanism, COAs are behaviorally undercontrolled (impulsive and sensation seeking) due to a combination of temperament, cognitive deficits, and poor parenting. Their behavioral undercontrol produces poor school performance, rejection by mainstream peers, and affiliation with drug using peers, which raise risk for drug use. The current analyses test whether behavioral undercontrol mediates the effect of parent alcoholism on risk for drug abuse and dependence.

Previous data are consistent with behavioral undercontrol as a mediator of parent alcoholism risk. COAs are impulsive and sensation-seeking, and these characteristics predict substance use disorders. However, there are few existing tests of mediation, and they are either cross-sectional or limited to alcohol disorders (for a review see Chassin *et al.*, in press). The current study tested whether behavioral undercontrol in adolescence mediated parent alcoholism risk for drug disorders in young adulthood; whether this effect could be explained by a correlated process in which behavioral undercontrol is itself transmitted intergenerationally, and whether maternal support in adolescence would buffer the risk associated with this pathway.

Alcoholic families were recruited from DUI records, HMO enrollments, and community phone surveys; control families were recruited using community phone surveys matching the target child in family structure, age, and gender (total N=454, agel2.7, see Chassin *et al.*, 1992). Three annual computer-assisted interviews were conducted with adolescents and parents, with a long-term follow-up at median age of 20. Measures of behavioral undercontrol included EASI and Revelle Impulsivity scales and sensation-seeking items, and maternal support items were adapted from the NRI. Diagnoses of parent alcoholism and young adult illegal drug abuse/dependence were measured with the DIS. Sample retention was 98% in the adolescent waves and 90% at long-term follow-up.

The first analysis examined whether behavioral undercontrol mediates parent alcoholism effects on later drug diagnoses. A logistic regression model prospectively predicted young adult drug diagnoses from parent alcoholism and adolescent behavioral undercontrol (impulsivity and sensation seeking) with gender and parent antisocial personality as covariates. Drug diagnoses were significantly predicted both by parent alcoholism and behavioral undercontrol, and there was a significant indirect effect of parent alcoholism mediated through behavioral undercontrol (Sobel's test). Behavioral undercontrol explained 22% of the parent alcoholism effect on diagnosis, but did not eliminate its significant effect. Thus, behavioral undercontrol was a significant but partial mediator of parent alcoholism effects. There were no interactions with gender.

Analysis two investigated whether there is correlated intergenerational transmission of behavioral undercontrol. A path analysis tested whether maternal and paternal alcoholism were correlated with maternal and paternal undercontrol (EASI scores), whether maternal and paternal undercontrol predicted adolescent undercontrol, and whether adolescent undercontrol predicted young adult drug diagnoses. Results showed that mothers' alcoholism was significantly correlated with mothers' undercontrol, and fathers' alcoholism was correlated with fathers' undercontrol. Moreover, mothers' undercontrol predicted adolescents' undercontrol, which predicted their drug diagnoses (a significant indirect effect). However, fathers' undercontrol was not significantly related to the adolescent's undercontrol. Rather, fathers' alcoholism predicted adolescent undercontrol, which indirectly predicted drug diagnoses (replicating the findings in Question 1 above with a different measure of undercontrol and a different year of measurement).

In the third analysis, we examined whether maternal support in adolescence buffers risk for later drug disorders. To test this question, we added maternal support and the interaction between behavioral undercontrol and maternal support to the logistic regression model described in Question 1 above, and this interaction was significant. Probing the interaction showed that the form of the interaction was "protective but reactive" (Luthar *et al.*, 2000) rather than classically buffering. That is, although maternal support reduced the risk for drug disorders, the protective effect was lost at very high levels of behavioral undercontrol.

Results suggest that behavioral undercontrol significantly but partially mediates parent alcoholism effects on the later development of drug abuse and dependence. COAs are at elevated risk for drug disorders in part, because of their impulsivity and sensation seeking. However, the partial mediation suggests that other pathways are also operative.

Moreover, for mothers, this process may involve the correlated intergenerational transmission of behavioral undercontrol, in which alcoholic mothers are themselves impulsive and sensation seeking, and directly transmit these characteristics to their children (perhaps through genetic transmission of temperament or through modeling). For fathers, this direct transmission of behavioral undercontrol was not supported. Perhaps fathers who directly transmit behavioral undercontrol to their children are under-represented in the sample because they leave the home before their children are adolescents. Alternatively, paternal alcoholism might elevate adolescent undercontrol through mechanisms other than direct transmission. For example, alcoholic fathers may expose their children to high levels of conflict, which alter their arousal levels and impair self-regulation.

Finally, maternal support in adolescence can be protective, but this protective effect is lost at high levels of behavioral undercontrol. Thus, adolescents who are extremely impulsive and sensation-seeking may derive little benefit from interventions designed to increase maternal support. This "protective but reactive" effect replicates findings obtained in studies of conduct problems in high risk populations (Wooten *et al.*, 1997) but differs from the classic buffering obtained in the general adolescent population (Stice and Gonzales 1998). Studies of high risk samples are an important complement to general population studies because they can illuminate processes that are operative at the upper end of the risk continuum but that might not be revealed in general adolescent samples.

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EPIGENETIC ANALYSES OF THE TRANSITION FOR NO SUBSTANCE USE TO SUBSTANCE USE TO SUBSTANCE USE DISORDER

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It is consensually recognized that the risk for substance use disorder (SUD) is not evenly or randomly distributed in the population. Research has revealed that a variety of biological, psychological and environmental factors are associated with a heightened risk for SUD. Genetic factors appear to contribute up to 50% of the variance underlying SUD risk.

This study was directed at determining the role of neurobehavior disinhibition (ND) in the risk for SUD. The contribution of ND in conjunction with drug use behavior, social maladjustment, family history of SUD and parental neglect of the child was examined. In addition, the P300 amplitude measured in an auditory "oddball" task was evaluated as a potential neurophysiological mechanism underlying ND.

The sample was based on high risk paradigm in which proband fathers with at least one son 10-12 years old were ascertained based on the presence/absence of SUD. The men were recruited from multiple sources using diverse methods to minimize the potential of accruing a biased sample. The probands who qualified for SUD satisfied either abuse or dependence criteria associated with an illicit compound or non-medical use of a prescription drug. Their sons were designated as the high average risk group. The probands without SUD were free of any adult axis I or II psychiatric disorder. Their Sons were designated as the low average risk group. In the two studies reported herein, the sample Sizes were 112 and 170.

The neurobehavior disinhibition construct was derived using indicators of executive cognitive functioning, difficult temperament, and disruptive behavior symptoms. Confirmatory factor analysis revealed an acceptable data model fit pointing to the unidimensionality of the construct. Social maladjustment and drug use frequency were assessed using Scales from the Drug Use Screening Inventory.

In Study #1, the ND score measured at ages 10-12 and age 16 predicted SUD outcome at age 19. As expected, prediction was stronger between ages 16 to 19 than from ages 10-12 to 19. In the former analysis, ND and substance use frequency predicted the transition to SUD at age 19 with *85%* classification accuracy. Sensitivity was 91% and the positive predictive value was 97%. Furthermore, the ND score accounted for *50%* of the variance on the overall problem density score of the Drug Use Screening Inventory. Notably, severity of ND increased from childhood (age 10-12) to mid-adolescence (age 16).

In Study #2, multivariate modeling revealed that SUD in the mother and father each predicted ND severity score in their biological son at ages 10-12 and 16 . In addition, ND had a direct association with SUD at age 19 and also a mediated relation via social maladjustment. Significantly, ND at age 16 was a stronger predictor of the transition to SUD than substance use behavior. SUD diagnosis in the parents did not predict severity of child neglect; however, this latter variable was a direct predictor of SUD. The P300 component of the ERP predicted ND score at age 16 which in turn predicted SUD at age 19.

The findings of this research indicate that ND is an important phenotype associated with SUD liability. These results are consistent with recent theoretical expositions implicating a dysfunction in prefrontal cortex underlying SUD risk. Employing an inductive process, the findings also indicate that ND and contextual factors conjointly promote SUD. Hence, a major task for investigators is to delineate the quality of ND (phenotype) and environment interactions during ontogeny that foster the development of SUD.

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PREDICTOR TRAJECTORIES AND SUBSTANCE USE PROBLEMS IN MID-ADOLESCENCE

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A nontrivial proportion of adolescents experience problems associated: with substance use, and studies have shown predictors of substance use level and problems (Pandina and Johnson 1999; Wills, Sandy, and Shinar 1999). Longitudinal research has predominantly relied on point prediction, testing variables from one point in time as predictors of change in substance use over a subsequent interval. However, it is possible that predictors themselves change over time, and change may be as informative as base level (Wills and Stoolmiller, 2002). Several predictor trajectories may exist, including stable and changing trajectories and also curvilinear or step functions. In theory, the trajectory of a predictor may influence problems through affecting endpoint level of the predictor or level of substance use; but pattern of change may also carry unique information. The present research tested this formulation with six variables drawn from different theoretical models; selected were academic competence, negative affect, anger coping, tolerance for deviance, family life events, and friends' alcohol use. We tested whether predictor trajectories were related to substance use problems and whether this occurred primarily through an impact on level of adolescents' substance use.

The data derived from a school-based study in which participants were surveyed at yearly intervals from 7th grade through 10th grade. The baseline sample of 1,702 participants (M age 12.4 years) was multiethnic and balanced on gender. Parents were informed about the research and students gave assent prior to questionnaire administration. The questionnaire was administered under confidential conditions and the data were protected by a Certificate of Confidentiality. Completion rates were 94%, 88%, 84%, and 83% for the first through fourth waves, respectively, with the majority of case loss occurring through student absenteeism. Retention of study variables over the four waves of data collection was approximately 70%. The predictor measures were 4-12 item scales with good reliability, and adolescent substance use was assessed with 4 items indexing tobacco, alcohol, and marijuana use (Wills *et al.*, 2002). Problems were measured with a 7-item scale on control/dependence problems and a 9-item scale on conduct/interpersonal problems (White and Labouvie 1989).

Clustering analyses were performed using disjoint clustering with SAS Proc Fastclus; solutions were replicated using agglomerative clustering with Ward's method. Clustering statistics indicated solutions in the range of 5-6 clusters were generally plausible; cell sizes were substantial and analyses were based on a 5-cluster solution for comparability across variables. Results for predictor trajectories showed there were typically a group that was stably high on the variable and a group that was stably low on the variable. Most solutions included one or more groups that increased over time on the variable, and typically there was a group that declined over time. Other clusters were U-shaped or step functions.

Analyses of variance (Anovas) tested the relation of predictor trajectories to substance use problems in mid-adolescence. Residual scores (i.e., the number of control or conduct problems not accounted for by an individual's level of use) were computed by regressing the 10th grade substance use score on control problems or conduct problems; these also served as criterion variables. Analyses were performed only for persons with a nonzero level of substance use, and included indices for demographic variables (gender, ethnicity, and family structure) to control for any relation of trajectories with demographic attributes.

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Some common themes were noted in the results. Taking academic competence as an example, individuals with a trajectory representing stable low risk (i.e., high competence) generally had few problems in mid-adolescence. Individuals with a trajectory representing stable high risk (i.e., low competence) generally had a high number of problems. It was also found that individuals in a trajectory representing decreasing risk over time (e.g., improvement in academic competence) had relatively lower problems even though they started at a relatively high risk level of risk. So change over time does matter. Individuals in a trajectory representing increasing risk over time had higher, sometimes much higher, numbers of problems. This was sometimes true for both control problems and conduct problems, as was the case for academic competence, but various predictors had effects on different types of problems. The effect of trajectory membership on problems was not consistently accounted for by level of use. Though levels of substance use differed across trajectories, the Anovas showed significant effects for residual scores, indicating an influence of trajectory membership that occurred above and beyond an impact on level of use. Distinctive effects were noted for particular variables but these are not discussed here.

Multiple regression analyses, entering trajectory membership and 10th grade value for the predictor simultaneously, indicated that in most cases trajectory information had a significant unique effect net of endpoint value for the variable. For substance use this was true for five of the six variables, and for substance use problems the majority of analyses indicated that trajectory information had a significant unique effect. So even though trajectory was correlated with endpoint value, the comparative analyses showed that history is important.

Thus, there is something about individual history that leads to substance use problems above and beyond other effects. Individuals who increased markedly in adolescence had more problems than persons with stable high-risk trajectories, so this type of trajectory carries substantial risk. Conversely, persons in trajectories that represented decreasing risk over time had low levels of use and large negative residuals in mid-adolescence; thus increasing competence and decreasing deviant peer affiliations can have a disproportionate effect on risk status and this finding has obvious implications for prevention programs. It should be noted that groups with stable high risk were not well off in mid-adolescence, and for some variables they were worse off, so attention to reducing risk among those with early-onset risk profiles should be advocated. A further question is why, among persons with similar starting values, some individuals declined in risk status whereas others remained at high risk (Glantz and Sloboda 1999). Such questions need to be investigated further.

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DEVELOPMENTAL PATHWAYS TO SUBSTANCE USE AND OTHER PROBLEM BEHAVIORS

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Research on developmental sequences in different forms of juvenile substance use shows substance use tends to unfold in an orderly fashion. However, it is also clear that different ethnic groups experience different sequences of substance use, and that most of the research to date focuses on the onset of any substance use rather than regular substance use. These points are important for theoretical and practical reasons, because interventions may have to be different for different ethnic groups. Also, different factors may predict regular use than any type of use. We will focus particularly on behavior problems as predictors of substance use, because of known links between aggression and alcohol use, depressed mood and marijuana use, and inattention and tobacco use.

The paper addresses two questions: (a) Do developmental sequences of regular use differ from sequences in my use and does this differ by race? (b) Does the presence of specific problems further explain individuals' progression to certain and not to other forms of regular substance use?

To answer the questions, we will use longitudinal data from the Pittsburgh Youth Study (PYS). The study began in 1987, and is now in its fifteenth year. The study consists of three samples of inner-city boys (1,517 boys in total) who had been randomly selected from the first, fourth, and seventh grades of Pittsburgh public schools (called the youngest, middle, and oldest sample, respectively). After an initial screening (85% of the randomly selected families participated), 30% of the most antisocial boys (based on parent, teacher and participant information) were included in the sample for follow-up, together with 30% randomly selected from the remainder. Just over half of the sample is African American, and the rest Caucasian. Over 90% lived with their natural mother. The boys are fairly evenly distributed across socio-economic levels. A screening formula allows us to weight the results of each of the samples back to the population prior to screening. The present analyses focus on the youngest sample (N = 503) from age 7 to 18 over 16 data waves.

The dependent variables are daily tobacco use, weekly marijuana use, weekly alcohol use, and hard drug use at a frequency of three or more times in the past year. The prevalence of regular alcohol use by African American and white males was not different, but more whites than African American males regularly used alcohol (48% vs. 39%) and hard drug use (16% vs. 2%), but the reverse applied to regular marijuana use (26% *vs.* 4 1%).

Cumulative onset graphs of substance use showed that the typical development sequence for whites was: alcohol, tobacco, marijuana, and hard drugs. In contrast, the sequence for African Americans differed by age. Prior to age 13, the most typical sequence was alcohol, tobacco, marijuana, and hard drugs, but after age 13, the sequence was alcohol, marijuana, tobacco, and hard drugs. When we examined developmental sequences n regular substance use, we found for whites that the following sequence was most common: tobacco, alcohol/marijuana (the two appear to co-occur), and hard drugs. For African Americans, the typical sequence of regular use was tobacco/marijuana (similar in onset), followed by alcohol use (too few were hard drug users to be included).

We next examined the forward probabilities of regular substance use. The probability that among whites nonusers would become regular tobacco users was .48, and that regular tobacco users would become regular alcohol and/or marijuana users was .46. The probability that regular alcohol/marijuana users would become repeat users of hard drugs was much lower (p = .15). The probabilities for African Americans were different in magnitude and type of use. The probability of nonusers becoming regular tobacco and/or marijuana users was .54, but the probability that regular tobacco/marijuana users would become regular alcohol users was .21.

We next address the question of which specific behavior problems could explain an individual's progression to certain and not to others forms of regular substance use. The best predictors of the transition from no use to regular tobacco use by whites were depressed mood and physical aggression. These factors also predicted African Americans' transition from no substance use to regular tobacco/marijuana use. We did not find that any of the three behavior problems predicted the next transition in regular substance use for either whites or African Americans.

The study has several caveats. We lost statistical power as we attempted to predict young men's transitions to regular substance use down the sequence of such use. Analyses did not take into account co-occurrence or reciprocal influences. We concluded that onset sequences of any substance use differ from onset sequences of regular use. Hazard slopes show that whites, compared to African Americans, are about two years ahead in their use of tobacco. Onset sequences differ somewhat between whites and African Americans. Physical aggression and depressed mood predicted the first but not the subsequent transitions toward regular substance use. If replicated, the findings have implications for the prevention of regular substance use by young males.

DISCUSSANT

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The four presentations in this session represent different, yet convergent, approaches aimed at examining important etiological factors linked to the development and expression of drug use behaviors and outcomes. Three of the projects (those described by Drs. Chassin, Tatter and Loeber) utilize variants of high risk paradigms, that is, they focus upon identifying factors at work in the expression of use behaviors and outcomes in young subjects selected from various sub-populations characterized as being at heightened risk for drug (and/or alcohol) use related outcomes. Tatter's subjects are children (age 10-12 at first measurement) selected on the basis of fathers' substance use dependence diagnosis. Loeber's sample of youthful subjects were selected on the basis of antisocial behavioral tendencies. Chassin's work focuses on differential developmental outcomes of children from families where parental alcoholism is prevalent. Of course, all three programs include appropriate contrasting control subjects and assess a wide range of putative moderators and mediators ("risk and protective" factors) that have been demonstrated to be linked to the developmental course of use behaviors. All three are excellent examples of well designed longitudinal research programs cast within a life span developmental framework. The work reported by Dr. Wills takes a some what different, though complimentary, approach in that his subjects are drawn from a school based sample more reflective of a normative population (at least in terms of risk profile). Wills' work also examines a broad set of risk and protective factors in relationship to use statuses. All four are attempting to build and test broader developmental models of substance use etiology.

Attempting to capture the nuances of the extensive programs of research summarized in this session's presentations is a significant challenge and it is likely that more will be omitted than included. Nevertheless, several key themes, perhaps better characterized as challenges, punched through as I reflected on the careful work of all four researchers. Embedded in these challenges are very real implications for prevention. A major issue is the need to characterize and capture the essential features of substance use behaviors (that is, use phenotypes) in a comprehensive yet parsimonious index. This problem is not trivial at either the theoretical, methodological or practical level, and each investigator in the panel has dealt with the problem somewhat differently. Often the differences in approach are appropriate to the nature of the underlying question of individual projects. What appears common is the attempt to capture both static and dynamic features of use behavior. Static features include horizontal and vertical organization usually focusing upon a single or brief time frame (e.g., at the time of assessment, last month, typical). Horizontal organization is often indexed as use stage (e.g., non-use, any use, onset, experimentation, regular) or may reflect movement (sometimes characterized as "progression") across drug type (tobacco to alcohol to marijuana to "hard" drugs). Vertical organization is often indexed by use intensity characterized in either quantitative terms (e.g., quantity and frequency of dose per unit of time) or qualitatively (e.g., regular, problem use, dependent use). Qualitative characterization may also reflect perceived or documented "harm potential"(e.g., toxicity, problem generation dependence liability,) of either a use intensity level, the quality of the drug or some combination of quantitative or qualitative dimensions. Note that these vertical and horizontal organizations are not always exclusive as in the case of using concepts such as "regular" use to characterize a horizontal stage as well as a use intensity.

Capturing the dynamic dimension is even more of a challenge. Typically, as is demonstrated in the researches reported here, investigators recognize the changing nature of use patterns across time and attempt to incorporate this feature into phenotypes (e.g., escalation, normative change, cessation, adolescent limited) often using rather sophisticated analytical techniques to capture the dynamism (e.g., growth curve analysis). That dynamism may also be reflected or recorded on different clocks (e.g., historical time, maturational growth, developmental stage) with differential impact. And, to make things just a bit more difficult, we have the issue of summarizing across a wide variety of substances (e.g., nicotine, alcohol, marijuana, cocaine, MDMA) in what seems to be an infinite array of patterns. Part of the challenge in indexing the phenotypes of use behavior is the attempt to identify theoretically meaningful, methodologically sound and practically useful points of transition in both horizontal and vertical features and static and dynamic dimensions of use. Thus, it is of major importance to separate out trivial fluctuations (e.g., true error variance, noise) in phenotypic expressions from those that signal meaningful transitions to qualitatively (and quantitatively) distinctive states. A related challenge is the identification of possible valid alternative development use trajectories inasmuch as research such as that presented today clearly indicates as much diversity as commonality in such pathways. In summary, capturing the nature of use behavior in all of its moving parts is a significant, ongoing and far from trivial challenge. This effort should be diligently monitored by prevention scientists as they need to remain constantly aware of the complex and changing nature of the phenotypes whose course they seek to alter.

A second major theme in these strains of research, is the attempt to identify, characterize and select putative markers, moderators and mediators that may index (mark), influence (moderate) or, in the best case scenario, determine (mediate) change (or potentiate likelihood, "risk", of change) in use states. Taken together as a class, these markers, moderators and mediators have been characterized as "risk and protective" factors. These run the gamut of biological, psychological-behavioral, socio-environmental influences. Further, as is the case with use phenotypes, these factors have both static and dynamic dimensions and features that are complex and difficult to capture in a single parsimonious index. As is the case for use phenotypes, it is likely that risk and protective profiles (or trajectories) are multivariate in structure and have important dynamic features. This fact makes it more difficult to identify such pathways. The story does not end there, however; the second part of the challenge is to identify and model the processes through which the putative factors affect transitions in use phenotypes. As noted, above, the four presenters have each chosen a variety of theoretically viable risk and protective factors to investigate depending upon the nuances of their theoretical orientations, sample (or subject) characteristics, use phenotype array, and structural characteristics and emphasis of the particular research project. Each investigator has attempted to craft carefully a well specified model that seeks to characterize the relationships between risk and protective profiles and complex use phenotypes. And, finally each has selected a variety of methods to assess the reliability and validity of modeled relationships. Prevention scientists should be particularly riveted on the results of this phase of their endeavors inasmuch as this information is the essential substrate for the development of interventions. It is the goal of prevention science to alter transitions in use phenotypes by identifying, intervening in, and altering the course of, factors that determine risk of such transitions. Hence, they must be cognizant of risk and protective factors and must seek to understand the manner in which (that is, the processes at work) they function.

The selection and assessment of risk and protective factors is itself a daunting task and, in this regard the presenters must be commended for the tenacity and judgment they have shown in selecting and evaluating key factors for their respective models. Why? At last count, there is empirical evidence supporting over 100 putative risk and protective factors with relevance for substance use etiology. Further, many of these have been linked to outcomes other than substance use, abuse and dependence. Hence, the process of selecting, sorting and, most significantly, empirically testing the viability (i.e., reliability and validity) of these factors in reasonable models is a difficult and important task. As part of the model building effort, each scientist has also sought to develop methods to seek a parsimonious solution to the "risk factor problem". It should be clear that not all factors can be tested by a single research team in a single focused study no matter how complex or elaborate. In fact, it may not be desirable, let alone feasible, to do so. The substantial gains in this area that are reflected in today's presentations suggest that the time is right for researchers in this area to develop a more formal method to coordinated and link evaluative efforts. It would be desirable and appropriate to infuse prevention scientists into this process.

This evaluative task should be appreciated and progress carefully followed by prevention scientists who should be concerned with selecting appropriate factors to modify and who wish to know how such factors express their influences. One of the other unrecognized, and, perhaps, undervalued, contributions of the type of research reported in this symposium is that the required evaluative efforts can lead to a better understanding of the structure of risk and protective mechanisms. One very important by-product would be the development of a taxonomy (akin to a periodic table of elements) of such factors as well as a better understanding of the manner in which they combine to exert effects, another potential gold mine for prevention scientists. A second important by-product is the development of novel and effective methods for identifying risk and protective profiles and assessing their reliability and validity. Much of this technology can also be applied to evaluate the outcomes of existing and novel prevention interventions.

A final major theme can be identified. This strain of longitudinal research is labor intensive but has an ongoing and evolving value yet unrealized. These projects represent ongoing treasure chests of information that cannot be easily reproduced, replaced or replicated in the foreseeable future nor, for that matter, in the lifespan of researchers currently in the field. The investment in time and effort, the scientific output and expanding knowledge base are truly remarkable. It was mentioned that one of the difficulties of this type of research is that the investigators grow at the same rate as the subjects. This makes for a long scientific incubation period, indeed! Thus, we must find a way to preserve these as living studies for future generations of researchers. This is a matter for serious consideration and suggests the need to do more than archive data sets for "secondary" analysis.

In summary, there are a number of important themes embedded in the presentations of this symposium. Themes that represent not only the individual projects reported on today but also reflect a growing body of literature. These themes should have special significance for prevention scientists who wish to refine and advance interventions. Some of the more major themes are: 1. Use phenotypes and risk and protective factor profiles are complex, multifaceted and dynamic in nature and are unlikely to yield to interventions targeted to static use stages or generic risk formulations; 2. Significant progress is being made in understanding the nature of mechanisms that link risk and protective profiles with use phenotypes and this advancing knowledge base can enhance greatly prevention approaches; 3. It is likely that a number of qualitatively and quantitatively differential and significant use phenotype-risk profile pathways will be identified, and equally probable that differential mechanisms link these trajectories will be discovered; this knowledge must be incorporated in the next generation of prevention interventions; 4. Comprehensive model building and testing will require cooperative efforts among researchers working with diverse populations, different theoretical frameworks and, possibly, competing models; 5. There is a need for greater linkage between etiological research and prevention science that permits rapid and on-going cross talk and translation of etiological research finding to prevention practice; prevention trials research offers the opportunity to "experiment" with models developed from etiological research but this can only happen within an environment of real and practical interchange; 6. Studies currently underway need to be preserved as living information treasures to be past on to subsequent generations of researchers.

SYMPOSIUM XI

DRUGS AND CRIME

R. A. Millstein and L. Erinoff, Chairpersons

This symposium, part of an ongoing collaboration between the National Institute of Justice and the National Institute on Drug Abuse, highlights some of the public health research issues relating to drugs and crime, with the aim of stimulating new research in these areas. Broad themes include crime, delinquency, epidemiology, developmental trajectories, and health disparities. Dr. Brownstein's presentation, analyzing Arrestee Drug Abuse Monitoring (ADAM) program data, discusses the utility of ADAM as a research platform. Dr. White's presentation explores developmental associations between drug use and delinquency. Dr. Anthony presents a new conceptual framework based on an epidemiologic field study approach to analyzing drug/crime relationships and also speaks to issues of race and ethnicity and also to demographic trends.

THE ADAM PROGRAM AS A RESEARCH PLATFORM

H. H. Brownstein and B. C. Taylor

National Institute of Justice

INTRODUCTION

The purpose of this paper is twofold: 1) to present recent findings on drug dependency and treatment in U.S. communities based on analysis of the Arrestee Drug Abuse Monitoring (ADAM) program of the National Institute of Justice (NIJ) and 2) to demonstrate the applicability and availability of ADAM data for research on drugs and crime. ADAM evolved from Drug Use Forecasting (DUF), which was started in 1987. DUF was intended to monitor nationwide trends in drug use among arrestees, provide local communities with early evidence of drug epidemics, and to support local planning with regard to problems associated with drug use and crime (Wish 1987). For both DUF and ADAM, 4 times each year in selected communities a local team of researchers interview and drug-test a sample of arrestees held in lockups and booking centers for a wide variety of offenses. In both cases, respondents are selected within 48 hours of arrest, and about 80% of arrestees asked to participate do so (Taylor *et al.*, 2001).

In the 1990's, when DUF was operational in 23 cities around the U.S., the early enthusiasm for simply knowing that large proportions of arrestees were using illicit substances at the time of their arrest gave way to concerns about the scientific efficacy of the program (Chaiken and Chaiken 1993; Caulkins *et al.*, 1999). ADAM was designed in response to those concerns. In particular, the number of sites was expanded; data collection was standardized (typically to the county level); probability-based sampling plans were implemented at each site; a new interview schedule was introduced to collect information about extended patterns of drug use, behavioral correlates, drug market dynamics, and drug dependence and treatment among arrestees (National Institute of Justice 2000). In 2002, the focus of ADAM shifted from expansion to research capacity.

DRUG USING AND DRUG MARKET DYNAMICS

In 2000, in 35 ADAM sites more than 50% of all arrestees tested positive for at least one of 5 drugs (median=64%). Arrestees tested positive for marijuana (median=41%) more than any other of the 4 drugs, followed by cocaine (31%), opiates (7%), methamphetamine (2%), and lastly PCP (0%). Interestingly, between the beginning of 2000 and the start of 2002, methamphetamine use among arrestees increased in ADAM communities from a median of less than 10% to almost 15%. However, throughout the period arrestees in western ADAM sites (e.g., Honolulu, Sacramento, San Diego) were nine times more likely to test positive for methamphetamine than arrestees in eastern ADAM sites, with many of those (e.g., Miami, New York, Philadelphia) having no arrestees testing positive.

Arrestees interviewed for the ADAM program are asked whether or not they obtained specific drugs in the 30 days prior to their current arrest. For each drug they say they obtained they are asked how often, whether or not they paid cash, how they obtained the drug, what method they used, where they got, was it a regular dealer, what they paid, and any difficulties they had. In calendar year most arrestees in most sites reported using something other than cash to obtain marijuana, crack cocaine, and powder cocaine. In almost all sites few arrestees reported having any trouble getting marijuana, crack, or powder cocaine when they wanted it. Except in a small number of sites drug sales most often took place outdoors, and in most sites most arrestees at least once in the past month had traveled out of their own neighborhood to get drugs.

DRUG TREATMENT AND DEPENDENCE AMONG ARRESTEES

Beginning in 2000, NIJ=s Arrestee Drug Abuse Monitoring (ADAM) program began collecting detailed information about the drug, alcohol, and mental health treatment experiences of respondents from probability-based samples of arrestees in counties around the U.S. Using a sophisticated calendar-based interview design, respondents were asked whether or not during the past year they had stayed at least one night in an inpatient or residential drug or alcohol treatment program, had been admitted to an outpatient drug or alcohol treatment program, and whether or not they had stayed for at least one night in a mental health treatment program. In addition, a screen was developed for the program with 6 items derived from the DSM-IV, to identify those among respondents who were at risk of drug or alcohol abuse or dependence (Hunt and Rhodes 2001).

In all communities with active ADAM programs in 2000, the median percentage of arrestees (of those who said they had used drugs) who were found to be at risk for drug dependence was 57%. The greatest proportion at risk for dependence were found in Honolulu (68%), and the lowest in Denver (45%). Despite that, few had participated in drug treatment in the past year. In terms of those who said they had participated in inpatient drug treatment in the past year, the median for all sites was 9% with the high being 17% (Albany, New York) and the low 4% (Birmingham, Alabama). In terms of outpatient drug treatment, the median for all sites in 2000 was 7%, with the high being 15% (New York) and the low 2% (Fort Lauderdale). Notably, for all sites, the median proportion of arrestees who said they had no health insurance was 67%. That is, ADAM data suggest that in communities around the United States there are large numbers of arrestees who are at risk of drug dependence, small numbers participating in any type of drug treatment, and large numbers who do not have health insurance.

ADAM AS A RESEARCH PLATFORM

The primary purpose of this paper is not to present ADAM findings. They are routinely reported in ADAM publications and on the ADAM website. Rather, the point here is to encourage others to make use of the ADAM data and the ADAM research platform. Different from DUF data, ADAM data are collected following established and accepted scientific standards, and are more comprehensive than DUF data. In addition, data are collected annually in selected sites, so over time are useful for both cross-sectional and trend analysis. And ADAM data are available to researchers through the Inter-University Consortium for Political and Social Research (ICPSR).

While DUF was originally designed to monitor drug using, ADAM was designed as a research platform. As a research platform, ADAM can be used in 3 different ways. (1) Data are available for secondary analysis. Using the core instrument, analyses can be conducted to address questions about the relationships between and among drug using, drug dependence, drug treatment, and drug market participation. (2) Working with particular ADAM sites, the ADAM platform can be adapted to particular research questions. For example, it is possible to oversample a particular category of arrestees to study a specific issue. Similarly, addenda questions can be added to the core instrument to study special topics as they relate to drugs, or the ADAM protocol can be implemented for a period of time in an area where ADAM data are not normally collected. (3) Though ADAM naturally cannot be used to directly address all the important questions about drugs and crime, findings from ADAM analyses do raise questions that can lead to other research that needs to be done.

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DISCLAIMER

Positions and points of view expressed herein are those of the authors and do not necessarily reflect nor represent the positions of the National Institute of Justice or the U.S. Department of Justice.

DEVELOPMENTAL PATTERNS OF DRUG USE AND CRIME

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INTRODUCTION

Several longitudinal studies have examined the developmental associations between drug use and crime, especially among adolescents, and the findings have been mixed (e.g., Huang *et al.*, 2000; Kaplan and Damphousse 1995; White and Hansell 1996, 1998; White *et al.*, 1999). These studies have primarily used variable-centered analysis techniques that examine the associations between drug use at one point in time and offending at another point, and, thus, make insufficient use of longitudinal data. Recently, criminologists and drug researchers have noted the value of person-centered analyses and have suggested that greater attention be directed toward individual growth curves and the description and explanation of intraindividual change. Due to recent advances in statistical techniques and the availability of new software, it is now possible to examine an individual=s behavioral trajectories over numerous time points using growth mixture modeling. Growth mixture modeling allows for identification of population heterogeneity in the level of a behavior at a given time, as well as in the development of the behavior over time. This approach can be used to examine the joint occurrence or comorbidity between two behaviors (i.e., drug use and illegal activity) simultaneously by relating the entire longitudinal course of the two behaviors. Thus, this approach allows for the examination of "the linkage between the dynamic unfolding of both behaviors over the entire period of observation, "makes use of all longitudinal measurements," and can capture "population differences in the strength and form of the comorbidity" (Nagin and Tremblay 2001, p. 20).

The purpose of this study was to examine the comorbidity between substance use and illegal activity from childhood into young adulthood. The first aim of this paper was to empirically identify and characterize different developmental trajectories of drug use and illegal offending from the ages 9 to 23 years. Then we examined the comorbidity between the trajectories. Although several studies have identified trajectories of offending and a few have identified trajectories of drug use, this is the first to look at trajectories of both behaviors in combination.

METHOD

Design and Sample. Data were collected as part of the Pittsburgh Youth Study (PYS), a prospective longitudinal study of the development of delinquency, substance use, and mental health problems (Loeber *et al.*, 1998). In 1987-88, random samples of first and seventh grade boys enrolled in the City of Pittsburgh public schools were screened. About 500 boys in each grade (the 250 most antisocial and another 250 randomly chosen from the remainder) were followed up 6 months later. After the first follow up, the boys were subsequently followed up at 6-month intervals for four or five additional assessments and then at yearly intervals for a total of 14 years. Attrition has remained relatively low. The sample is more than half African American, with the remainder almost all white. In addition, over one third of the participants= families received public assistance or food stamps.

Measures. The data for this analysis come from self-report questionnaires from the subjects, although the PYS has collected data from multiple sources. For drug use, at each age we sum the total number of times that participants have used a variety of illicit drugs and licit drugs for nonmedical purposes during the past year. For illegal activities, at each age we sum the total number of times that participants have engaged in a variety of serious and minor property and violent offenses during the past year. Note we did not include drug crimes, such as dealing.

Analyses. To take advantage of the cohort sequential design, age scores for each of the problem behaviors are used to model the trajectories. Data from the two cohorts are combined to create a developmental age sequence from age 9 to age 23 years. There is overlap of measures from the two cohorts for age 13 through age 18 years. We used Proc Traj, a customized SAS macro, to conduct the analyses (Nagin and Tremblay 2001). First we separately developed trajectory groups for drug use and offending by testing up to seven models for each behavior using a Poisson model. The second step in the analyses involved conducting joint trajectory analyses, which provides information on the comorbidity of the two behaviors over time.

RESULTS

Based on the Bayes Information Criterion (BIC), a six group model fit the data best for drug use: 1) nonusers (45%), 2) low level users (6%), 3) adolescence-limited users (12%), 4) later onset, escalating heavy drug users (8%), 5) medium onset heavy drug users (13%), and 6) early onset heavy drug users (15%). The BIC results indicated that a seven-group model best fit the data for offending: 1) nonoffenders (43%), 2) very low-level offenders (19%), 3) early peak adolescence-limited offenders (8%), 4) later peak adolescence-limited offenders (9%), 5) early onset, adolescence-peak chronic offenders (8%), 6) adolescence high-level offenders who decline by 19, but appear to be on an upswing in early adulthood (6%), and 7) chronic high level offenders who are dropping off in early adulthood (7%).

Examination of the trajectory groups across behaviors indicate that drug use and delinquency follow varied developmental courses in terms of onset and level. For all groups of offenders, offending starts by age 9 years. In contrast, drug use onset differs considerably across groups. Adolescence-limited drug users begin first, around age 12 years, whereas the three high-level groups begin at three different points in adolescence, age 14, age 16 and age 18 years. Offending peaks at different times. Two groups peak in early adolescence, one group in mid-adolescence, and two groups peak in late adolescence. In contrast, all drug-using groups, except the adolescence-limited group, peak in late adolescence. The adolescence-limited group maintains the same level of use from early to late adolescence. All high-level offenders reduce their frequency of offending in young adulthood. On the other hand, high-level drug users maintain their levels into young adulthood.

We examined the comorbidity of the two behaviors by examining the probabilities of being in the various drug use trajectory groups conditional on being in the offending trajectory groups and the probabilities of being in the various offending trajectory groups conditional on being in the drug use trajectory groups. The data show that involvement with drug use is not conditional on offending, although noninvolvement is somewhat conditional on nonoffending. In contrast, offending is more conditional on drug use than drug use is on offending. Overall the data show that the overlap in the developmental courses between these two behaviors is not that strong.

CONCLUSIONS

The results indicated that there were meaningful differences among trajectories groups as a function of age, developmental period and magnitude of drug use and offending. Thus, these groups can be used in future research to address many important issues in drug/crime research.

This research represents only an initial step in trying to explain the developmental patterns of drug use and crime. There are several limitations to the present study that need to be addressed in our future analyses. First of all, we used self-report data and combined both minor and serious offenses into our illegal activities measure. In our future research, we will separate them as well as look at differences between property and violent offenses. It will also be informative to compare trajectories based on self-report to those based on official arrest reports. Second, we combined all the drugs into one measure and did not include alcohol. Obviously, not all of the drugs included can be expected to be related to offending and their individual trajectories are likely to differ. Therefore, it will be interesting to examine trajectories of alcohol use and compare them to those for marijuana and other drugs, such as cocaine. Then these separate drug trajectories can be analyzed for their comorbidity with different types of crimes. In addition, it will be important to examine temporal sequences across these trajectories.

A major value of trajectory group analysis is for the identification of predictors and consequences of various developmental trajectories. Therefore, we plan to examine the impact of time invariant and time varying risk factors on these trajectories and to document the factors that may trigger transitions in trajectories. We will also examine differences in adult outcomes for various trajectories. With these trajectories groups it will be possible to examine subgroups of drug users and offenders to test independent hypotheses. Other analyses planned for the future include: controlling for time in jail, examining how arrests and other natural interventions affect trajectories, developing trajectories separately by race and examining the mediating and moderating effects of drug dealing. In sum, analysis of developmental trajectories utilizes longitudinal data efficiently and provides the opportunity to address many of the important questions facing drug/crime researchers in the 21st Century.

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NEW DIRECTIONS IN DRUGS & CRIME RESEARCH

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The main purpose of the discussion of these papers was to draw attention to some important advances represented in the refined ADAM procedures for surveillance and new research on drugs and crime relationships, and in the application of recent computational and statistical advances that can help us see these relationships more clearly. Anthony proposed a conceptual model that his research group developed in order to evaluate, guide, and plot its forward progress toward greater understanding and new discoveries about drug dependence epidemiology. He illustrated the applicability of this conceptual model to the domain of drugs-crime research (for more complete discussion, see Anthony with Forman 2002). He also pointed out some of the shortcomings of this model, particularly with respect to its capacities to highlight interactions that might be important (e.g., gene-environment interactions), and with respect to some very important allied lines of inquiry about the drugs-crime relationship such as ethnographic research. It is not that the conceptual model fails to allow for gene-environment interplay or other relationships or that it fails to accommodate ethnographic research. The model simply does not highlight these domains or lines of inquiry, and for this reason special annotation is needed.

In specific comments on the two papers in the session, Anthony remarked:

* For reasons described by Henry Brownstein and others, some of the early hopes for the Drug Use Forecasting system have not played out as expected. For example, DUF data has not been particularly useful as a general lead indicator of later trends in general population drug-taking behavior. However, especially with the refinements of DUF and its renaissance in ADAM, we have a more useful surveillance tool for investigations of the drug-taking behavior of individuals who are apprehended and brought to criminal justice intake facilities. It would be a pity if we were to stop gathering ADAM data now that these refinements are in place. The international perspective on drug surveillance in the United States generally is one of envy because of the refinements and our sustained support of consistent trend data. ADAM is one of the gems in this crown of drug surveillance, along with the National Household Surveys, Monitoring the Future, and DAWN. By definition, these are 'surveillance' tools, characterized more by their practicality, timeliness, and capacities to guide and encourage more probing research; less by their complete reliability and accuracy (Manski *et al.*, 2001).

* Helene Raskin White's presentation is especially important because it helps to show how careful longitudinal data analyses can disclose fine-grained details about trajectories of development, as the drugs-crime relationships play out over time. Some observers say that there is nothing new under the sun in this domain of drugs-crime research. These observers simply fail to appreciate the impact of late 20th century developments (e.g., see Gordon Moore's 'law' with respect to exponential growth in the number of transistors on a chip and the much-reduced costs in advanced computation). Because of these technological advances, we now are able to use statistical approaches with far greater resolving power than had been true in the past. Much of what we learned about statistical approaches in graduate school before 1978 and the introduction of the 8086 desktop system with 20,000-30,000 transistors per chip simply does not apply at the turn of the 21st century with Pentium IV systems having more than 40,000,000 transistors per chip. Much of the statistical theory and some of the computational software to help us gain greater resolving power were in place in 1980, but the computational power was too expensive for NIDA or NIJ research groups to make much progress. With more affordable computational power, the statistical theory and computational approaches are progressing in leaps and bounds, and we now are beginning to see the yield of this greater resolving power of new statistical approaches such as the longitudinal latent growth models illustrated in the work of the NIDA- and NIJ- supported Rutgers research group. This transformation is not exactly the same as the shift from the early lens used by van Leeuwenhoek and Galileo to the resolving power of an atomic force microscope or scanning/tunneling electron microscope, but there is an analogy here. For phenomena such as longitudinal growth trajectories, the statistical approaches available in 1980 simply did not have the resolving power of current statistical approaches, and we could expect even better resolving power in these 'microscopes' for research on drugs-crime relationships if there were even greater federal investment in the work of the 'basic' biostatisticians and statistical methodologists whose attention is necessary before more 'applied' social, behavioral, and epidemiological scientists can make use of these new methodological tools.

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SYMPOSIUM XII

VIOLENCE EXPOSURE AND SUBSTANCE ABUSE

W. Kliewer and D. Svikis, Chairpersons

INTRODUCTION

A growing body of evidence has documented associations between violence exposure and substance abuse. That is, individuals exposed to violence have higher rates of drug abuse than individuals without violence exposure. This relationship is robust, and has been found in both adolescents and adults not only in the United States, but internationally as well. Despite growing evidence that violence exposure increases risk for substance use and abuse, little is known about *why* or *how* this might occur. Research is needed to identify risk factors that may impact a person's risk for developing a substance use disorder in the face of violence exposure. One promising area of study may be gender and how it affects the relationship between violence exposure and substance abuse.

The purpose of this symposium was to examine the relationship between violence exposure and substance abuse from both epidemiologic and clinical perspectives, and to review current models of the association between the two constructs. Specifically, Dr. Kilpatrick reported on data from a national survey of adolescents linking exposure to violence and risk of substance abuse. Drs. Velez and Peirce discussed assessment and intervention for violence exposure in pregnant women attending substance abuse treatment. Dr. Kliewer described current models of the relation between violence exposure and substance use and abuse. Finally, implications for future research were discussed.

VIOLENCE EXPOSURE AND SUBSTANCE USE AND ABUSE IN ADOLESCENTS*

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There is a fair amount of retrospective data from studies of adult women that show that history of victimization during childhood or adolescence increases the risk of substance use, abuse, and dependence (e.g., Breslau *et al.*, 1991; Burnam *et al.*, 1988; Cottler *et al.*, 1992; Kessler *et al.*, 1995; Kilpatrick *et al.*, 1992; Kilpatrick *et al.*, in press). Other retrospective data from adult women show post-traumatic stress disorder (PTSD) increases the risk of substance use, abuse, and dependence, and violent assault is more likely to produce PTSD than other types of traumatic events (e.g., Kessler *et al.*, 1995; Kilpatrick *et al.*, 1992).

Although many adults report having used substances and having been victimized prior to age 18, no published study to date has assessed substance abuse and dependence, victimization history, and PTSD in a large nationally representative sample of male and female adolescents while also attending to gender differences. The first presentation summarized findings from The National Survey of Adolescents (NSA). The purpose of the presentation was to: 1) compare male and female adolescents with respect to rates of past year substance abuse and dependence; history of sexual and physical assault and witnessing violence; and lifetime and current PTSD; 2) determine the extent to which gender, victimization, and PTSD are risk factors for substance abuse/dependence among adolescents; and 3) determine if risk factors for substance abuse/dependence differ for male and female adolescents.

The sample consisted of a national probability household sample of 3,161 adolescents between the ages of 12 and 17 and an over-sample of 862 adolescents from households in the central cities as designated by the U.S. Bureau of the Census. Total sample size was 4,023. An area probability sampling strategy was used in which telephone exchanges within Census regions and size-of-place strata were identified. Next, randomly generated telephone numbers within each stratum were called to locate households with adolescents. The number of households sampled, were proportional to the population of adolescents in the stratum. Next, a parent or guardian was interviewed via telephone, and permission was obtained to interview a randomly selected adolescent within each household. Out of 5,367 eligible households, 4,836 parents completed interviews (90.1% of eligible households),

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4,326 parents gave permission for adolescent interviews (78.9% of eligible households; 87.6% of parents interviewed), and 4,023 adolescent interviews were completed (75% of eligible households; 83.2% of households with completed parent interviews; 95% of households with parental permission).

There were statistically significant gender differences in the lifetime prevalence of all types of sexual contact except others' mouth on sexual parts. In all cases, females were more likely to have had sexual contact (all $p < .0001$) than males. For example, sexual parts being touched or being forced to touch others' sexual parts occurred to 2.8% of the males and 9.9% of the females. Rates of any sexual assault were 3.4% for males and 13.0% for females. In contrast, lifetime prevalence of physical assault was significantly higher in males versus females, with the exception of being attacked with the intent to injure or kill. Six percent of males and 3.4% of females had been attacked with a weapon. Being beaten with fists and hurt badly occurred to 7.4% of males and 5.1% of females. For any physical assault the rates were 21.3% for males and 13.4% for females. Likewise, most forms of witnessing violence were higher for males versus females, with the exception of seeing someone sexually assaulted. For all forms of witnessing violence, lifetime prevalence was 43.6% for males and 35.0% for females ($p < .0001$). Lifetime and current prevalence of PTSD was significantly higher among female than among male adolescents. Past year prevalence of substance abuse or dependence was significantly higher in male than in female adolescents and was noteworthy within this adolescent sample (20% vs. 11% at the highest ages).

Rates of past year abuse or dependence on any substance were affected by victimization risk factors, lifetime and current PTSD, and gender. In univariate analyses, risk factors for past year substance abuse and dependence were increased age, sexual assault, physically abusive punishment, witnessing violence, PTSD, and gender. For example, 25.9% of adolescents with current PTSD had a substance abuse problem, whereas only 5.9% of adolescents without current PTSD had such a problem. Poverty and race were not risk factors at the univariate level. In multivariate analyses conducted separately among male and female adolescents, risk factors for substance abuse and dependence varied by gender. For females, risk factors included increased age, race (being Caucasian), sexual assault, witnessing violence, and PTSD. For males, risk factors included increased age, race (being Caucasian), physical assault, witnessing violence, and PTSD. Age and Caucasian racial status were larger risk factors for males versus females; witnessing violence was a larger risk factor for females.

The timing of substance use and victimization is an important factor to consider in attempting to explicate pathways to substance abuse. Among victims of violence who also had substance abuse or dependent problems, only about a third reported any alcohol or drug use prior to the year in which they were victimized, but almost half said their first substance use occurred following their first victimization.

Overall, these findings from the NSA demonstrate that violence exposure, both victimization and witnessing violence, and PTSD increase the risk of substance abuse and dependence. However, these data are correlational and therefore do not demonstrate causality. Longitudinal research is needed to track the temporal sequence of violence exposure and substance abuse and dependence.

CLINICAL TREATMENT-BASED RESEARCH: ASSESSMENT AND INTERVENTION FOR VIOLENCE IN PREGNANT WOMEN ATTENDING SUBSTANCE ABUSE TREATMENT[b]

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For women of childbearing age, the co-occurrence of substance abuse problems and intimate partner violence (IPV) has been well established (Augenbraun *et al.*, 2001; El-Bassel *et al.*, 2002; Gilbert *et al.*, 2001; Kalichman *et al.*, 1998). The majority of studies have found increased prevalence of IPV in women seeking substance abuse treatment, with lifetime prevalence rates ranging from 60 – 75% (Dunn *et al.*, 1994; Gil-Rivas *et al.*, 1996; Resnick *et al.*, 1993). These rates are two to three times higher than the 17% to 39% range found in national surveys of women (Browne 1993; Caetano 2001).

In epidemiological research, little is known about rates of IPV during pregnancy and potential patterns of co-morbidity with substance use disorders. Studies of IPV in pregnancy target fairly narrowly-defined, population-based subgroups of pregnant women. Taken together, however, such state and community-based studies of pregnant women report IPV prevalence rates ranging from 4 - 14 percent (GAO 2002; Gazmararian *et al.*, 1996). Less is known about IPV and substance use in pregnant women. In studies that identified pregnant women experiencing IPV through prenatal care clinics, found alcohol and drug use was more prevalent among women experiencing IPV than among women without such problems (Amaro *et al.*, 1990; Martin *et al.*, 1996).

Research has shown, that pregnant women who experience IPV are at increased risk for medical, obstetrical, nutritional and psychological problems. Although a causal relationship has not been established between violence during pregnancy and perinatal outcomes (Gazmararian 2000), elevated rates of spontaneous abortion, prematurity, sexually transmitted diseases (STDs), anemia, and low birth-weight have been found in women exposed to perinatal violence (Amaro *et al.*, 1990; McFarlane *et al.*, 1996a; 1996b; Parker *et al.*, 1993). Such women also tend to seek prenatal care later in pregnancy and are more likely to report psychiatric symptoms including depression, anxiety, and PTSD (Deren 1986; McFarlane *et al.*, 1996; Scallet 1996). Pregnant women with IPV also present with more frequent concerns for personal safety (e.g., they are at higher risk for homicide), and a myriad of needs in such domains as housing, parenting, financial aid, and legal issues.

Children who experience or witness violence are at risk for emotional, behavioral, social, and developmental problems. Traumatized infants and toddlers often display symptoms of reactive attachment disorder and PTSD. They are also at increased risk for becoming substance abusers, batterers, or victims of violence during adult life (De Bellis 2002).

When substance abuse and IPV are co-morbid within an individual or within a family system, it is often difficult for clinicians to reach consensus about specific treatment goals and their prioritization. Clearly, however, one disorder cannot be treated in isolation from the other; both must be addressed. Active substance abuse by the perpetrator or victim of domestic violence threatens the safety of the victim and can perpetuate or intensify IPV. Similarly, research has shown that IPV impairs the recovery process and threatens sobriety.

One area which has received almost no research attention is of IPV and substance abuse/dependence. This symposium presentation summarized data from a research and evaluation study of pregnant substance abusing women with IPV. The project is one of four funded by the Human Resources and Services Administration (HRSA) and the Maternal and Child Health Bureau. The goal of the project is to develop and subsequently evaluate a protocol for routine screening and systematic assessment for IPV in a sample of pregnant substance abusing women. Participants were pregnant drug abusing women admitted to a specialized program in Baltimore, MD. The program offered residential as well as intensive outpatient drug treatment services, with on-site OB/Gyn, family planning, and pediatric/childcare services (see Jansson *et al.*, 1996 for description).

Screening for IPV in Pregnant Substance Abusing Women

Systematic screening for current and lifetime exposure to IPV occurred using the Violence Exposure Questionnaire (VEQ). The VEQ was developed by study investigators, using the 4-item Abuse Assessment Screen (Helton 1986) as the initial template. In addition, the VEQ expanded survey items to include seven domains: physical abuse; sexual abuse; emotional abuse; perceived safety of patient; presence of weapons in the home; community violence exposure (self and children); and perceived need for help (self and children) for issues related to intimate and/or family violence. Responses are primarily categorical (e.g., yes/no), with several continuous measures (e.g., age of onset). Women were asked to complete the VEQ shortly after participating in a residential group counseling session that specifically focused on intimate/family violence and substance abuse.

Participants and Recruitment

From September 2000 to February 2002, 391 pregnant women completed the VEQ as part of standard treatment procedures. Demographically, the women were predominantly African American (69.4%), with a mean age of 29.42 years (5.28 SD). On average, the women reported 2.50 (SD 1.80) children. The number of children in their custody on admission, however, was significantly lower, with an average of 1.23 (SD 1.29) children per woman.

Analyses of VEQ questionnaire data found high rates of lifetime and current exposure to violence for both the women and their children. Lifetime rates of various types of violence ranged from 43% (sexual abuse) to 66% (emotional abuse) to 71% (physical abuse). Women often reported violence exposure continued during pregnancy with rates that ranged from 7% (sexual abuse) to 39% (emotional abuse) to 19% (physical abuse). Approximately one-third (34%) of the sample reported a recent history of physical fights with their partners and 17% reported such fights occurred in front of their children. Over one-half (56%) had a recent history of yelling or screaming fights with their partner; nearly one-fourth (24%) stated this occurred in front of children. Eleven percent felt unsafe at home and 25% reported a weapon available at home, and 43% reported such weapons included guns. Sadly, gun availability and experiencing a beating during pregnancy are both potent predictors of femicide (Campbell *et al.*, in press).

IPV Assessment

Follow-up for women reporting recent violence exposure and consenting to participate in assessment for problems related to their violence exposure involved administration of one or more of the following assessment tools:

1) Danger Assessment (DA) (Campbell 1986),
2) Symptom Checklist-90 Revised (SCL-90R) (Derogatis *et al.*, 1973),
3) Post-traumatic Stress Diagnostic Scale (PDS) (Foa *et al.*, 1993), and
4) Needs Assessment Questionnaire (NAQ) developed specifically for this protocol.

The majority of women who agreed to assessment completed all four of these measures. Also, SCL-90R data were available for women with and without violence exposure (N= 223) as it is part of standard care for all women admitted to the Center for Addiction and Pregnancy (CAP).

Danger Assessment. The DA is a 15-item yes/no questionnaire developed to help women assess their risk for lethality in an abusive intimate partner relationship. Recent studies (Campbell *et al.*, in press) suggest that women who score $\geq$4 are at serious risk for becoming a homicide victim and counselors are urged to argue assertively for safety planning. At the time of our analysis, DA data were available for 67 women reporting IPV and currently living and/or having contact with their abuser. The mean DA score was 5.48 (SD 3.16), with three-fourths of the sample (75%) scoring above four, suggesting this sample of women is at serious risk for homicide.

Symptom Checklist-90 Revised. The SCL-90R is administered to screen the psychological problems and symptoms of psychopathology and current global distress of the patients. This self-administered tool is used in the formulation of individualized plans for the patients regarding the need for psychiatric referral, individual counseling or referral to focus groups (e.g., anger management, self-esteem, etc). Women reporting current IPV evidenced higher levels of emotional distress than women without current IPV for 8 of the 9 SCL-90R scales (all $p<.05$). Women with IPV also obtained higher Global Symptom Index (1.20 vs. 0.93) than women without IPV ($p<.05$).

Post-traumatic Stress Diagnostic Scale. The PDS is administered to assess the presence and symptom severity of PTSD. One-half of substance-abusing pregnant women reporting violence exposure and accepting referral for violence-related counseling met criteria for co-morbid PTSD. Women with PTSD reported greater impairment across several domains of daily life functioning than women without PTSD.

Needs Assessment Questionnaire. The NAQ is administered to determine the needs for assistance on housing, social services, legal, parenting, and other social issues. This questionnaire also evaluates if the mothers perceive their children are having any behavioral, emotional and/or academic problem and their perception of need for help with these problems.

The findings of all assessments are explained to the patient and an individualized plan formulated and integrated with the substance abuse treatment plan. Each individual plan is developed and implemented according to each woman's readiness to engage in her individualized recommended plan for treatment, and after setting priorities regarding violence or substance abuse issues. Nearly two-thirds (65%) of women with current violence exposure received help finding a safe place to live and one-fourth (25%) received assistance designing a safety plan. Nearly one-half (47%) of these women needed help with parenting and over one-half (56%) admitted a need for a psychiatric referral for themselves. Interestingly, 14% of women with violence exposure felt they needed and received an immediate psychiatric referral for their child(ren).

Project Evaluation

Several standard care measures were used for preliminary evaluation of the effectiveness of this screening and assessment/referral based-intervention model. They included: positive urinalysis drug toxicology, length of stay in substance abuse treatment, and group attendance. To create the comparison groups, women were first classified as either IPV positive (recent disclosure of IPV) or IPV negative (no report of IPV). Those in the IPV positive group were subsequently divided into those who received intensive IPV services and those who received only standard drug treatment.

> *Group 1:* N=74 women reporting current IPV and receiving intensive IPV assessment/intervention services (i.e., individual IPV counseling, safety planning, case management for housing, legal issues, parenting, and/or psychiatric referrals for self or children). Group 1 also received "standard drug abuse treatment services" which included substance abuse treatment plus a weekly psycho-educational group that focused on IPV/substance abuse issues that was added to the curriculum as part of the HRSA-funded project.
>
> *Group 2:* N=92 women reporting current IPV but receiving no specialized (intensive) IPV services because they either chose not to participate or left treatment prematurely. Group 2 received the same "standard drug abuse treatment services" as Group 1.
>
> *Group 3:* N=145 women denying recent exposure to IPV. Group 3 also received the same "standard drug abuse treatment services" as Groups 1 and 2, including the weekly HRSA-sponsored psychoeducational group described above.

Analysis of variance (ANOVA) for the 3 groups found no differences for any demographic or psychosocial measure. Women in the three groups also reported similar "primary drugs of abuse", with heroin and cocaine being most prevalent. However, Group 1 women (IPV and intensive intervention) had significantly better outcomes than Group 2 and Group 3 women, with longer treatment retention (86.3, 52.3, and 42.7 days, respectively), more individual and group counseling sessions (171.6, 103.8 and 88.6 sessions, respectively) and a lower percentage of drug positive urinalysis screens (37.2%, 46.0%, and 56.7%, respectively) (all $p<.01$).

Preliminary findings suggest: 1) substance abusing pregnant women and their children have increased rates of exposure to violence; and 2) it is important that treatment programs which serve pregnant and postpartum women establish methods for routine patient screening for lifetime and current exposure to violence. The data also support the notion that provision of specialized intervention and assessment services for pregnant substance dependent women with IPV may contribute to longer rates of treatment retention, reduced drug use and improvements in psychosocial functioning.

The data presented above must be interpreted with caution. First, sample sizes remain small and this is a preliminary analysis. Second, this was not a random assignment study, therefore, patient self-selection factors cannot be ruled out. While IPV and non-IPV women were comparable for most demographic variables, other factors not measured in this project may play a role in the observed group differences (e.g., patient motivation) and warrant further study.

In conclusion, the study data support the importance of routine screening for IPV in women of childbearing age (and in particular, pregnant and postpartum women). Follow-up assessment, intervention and referral are also critical. Staff often feel unprepared to deal with such issues, however, which supports a need for staff training in substance abuse and IPV, with particular attention paid to the myriad of issues that arise when violence and addiction co-occur in a pregnant woman.

CURRENT MODELS OF THE RELATION BETWEEN VIOLENCE EXPOSURE AND SUBSTANCE ABUSE

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Violence exposure is one type of stressor that places individuals at increased risk for substance use, abuse, and dependence. Violence exposure may take many forms, including witnessing community violence or domestic violence, or being victimized physically or sexually. Violence exposure can impact an individuals' sense of fairness and safety, as well as challenge perceptions of control (Garbarino *et al.*, 1992).

Coping is defined as cognitive and/or behavioral efforts to change the situation or to manage one's affective responses to it (Lazarus and Folkman 1984). Coping presumes the existence of stress, and is not equated with success; some coping efforts may be maladaptive and unsuccessful. Substance abuse may be conceptualized as a form of maladaptive coping. It is important to note that coping is multiply determined, as is substance abuse and dependence. Both coping in general and substance abuse in particular are influenced by genetic predispositions, family socialization, and other environmental influences (such as peers). The risk of using substances to cope following violence exposure varies markedly from person to person. The variation in individual risk of substance abuse to cope with violence is important to study for both theoretical and practical reasons.

There are several ways to think about the connections between violence exposure and substance abuse and dependence. *Mediator Models* specify the process by which violence exposure leads to substance abuse. This information is particularly important when developing interventions designed to reduce maladaptive coping in response to violence exposure. *Moderator Models* specify when and for whom there is a relation between violence exposure and substance abuse. This information is particularly important when resources are scarce and interventions need to be targeted at groups who are most in need of intervention and who would most benefit from it.

PTSD and physiological arousal have been identified as potential mediators or moderators of the relation between violence exposure and substance abuse. PTSD is a constellation of symptoms resulting from exposure to trauma. These symptoms include re-experiencing the event, avoidance or numbing, and increased arousal. A model that specifies PTSD as a mediator suggests that the reason violence exposure is associated with increased risk for substance abuse is that violence exposure increases symptoms of PTSD, which in turn increase substance abuse. Although there is some tangential evidence in literature that PTSD may indeed mediate the relation between violence exposure and substance abuse, this model has not been formally tested. An alternative model posits PTSD as a moderator of the relation between violence exposure and substance abuse. In this model, violence exposure is hypothesized to have the greatest risk for substance abuse among persons with PTSD. Thus, PTSD in the presence of violence exposure magnifies the risk that would be attributable to violence exposure and PTSD independently. This hypothesis has not been formally tested in literature, although researchers have shown both violence exposure and PTSD are risk factors for substance abuse and dependence.

Less research has been conducted with physiological arousal as a mediator or moderator of the relation between violence exposure and substance use, abuse, and dependence. A model with physiological arousal as a mediator suggests violence exposure is associated with physiological arousal, which in turn is related to substance abuse. This model suggests the reason violence exposure is associated with increased risk for substance abuse is violence exposure affects physiological responses. Although there have been no formal tests of this model published to date, work by Moss *et al.*, (1999) suggests that preadolescent boys who showed a *dampened* physiological response to an acute laboratory stressor were *more* likely to report marijuana use four years later. Thus, it may be that youth who show a dampened physiological response to chronic violence exposure are at greatest risk for substance abuse in the future. Why this pattern exists is unclear. An alternative model, the moderator model, suggests that magnitude of the relation between violence exposure and substance abuse is affected by a person's propensity to be physiologically aroused. Unlike the model with PTSD as a moderator, because of the dearth of research on this topic it is unclear whether hypoarousal or hyperarousal to stress places individuals at greater risk for substance abuse in the face of violence exposure.

There are very few studies that examine associations between violence exposure and physiological arousal. Wilson, Kliewer, and their colleagues (in press), studied the relation between violence exposure and ambulatory blood pressure (BP) in 56 African American teens, all of whom had normal BP, were within 25% of their ideal body weight, and were not taking medication. Questionnaires were used to assess youth's experiencing, witnessing, or hearing about violence. Youth wore a BP monitor for 24 hours to assess ambulatory BP. Heart rate and BP readings were obtained every 15 minutes. Measures of daytime and nighttime BP were obtained from the output. Daytime and nighttime epinephrine and norepinephrine were obtained as well from urine samples. Youth were classified as *non-dippers* if their BP failed to drop 10% or more from daytime to nighttime. Non-dipping is an independent risk factor for cardiovascular disease. Logistic regression analyses revealed that victimization was associated with non-dipping (i.e., failure of BP to drop at night) in both males and females. For males only, hearing about violence was associated with non-dipping. Hearing about violence also was associated with daytime epinephrine in males ($\underline{r}$ = .59) but not in females ($\underline{r}$ = .03).

In a second study of violence exposure and physiological arousal, Diehl and Kliewer (2002) used salivary cortisol to index physiological arousal. Participants were 101 African American 9 to 13-year olds who lived in moderate to high violence areas of Richmond, VA. Violence exposure was assessed via face-to-face interviews. Cortisol samples were obtained 3 times during the laboratory visit. Victimization was positively associated with average cortisol levels in males ($\underline{r}$ = .45) but not in females ($\underline{r}$ = 0). Likewise, hearing about violence was positively associated with average cortisol levels in males ($\underline{r}$ = .34) but not females ($\underline{r}$ = .16). The fact that different patterns of association between violence exposure and physiological arousal were observed for males and females in these two studies suggests that gender should be included as an additional moderator in this research.

CONCLUSION

In summary, there is strong evidence that violence exposure is associated with substance abuse and dependence in both epidemiologic and clinical samples. There is emerging evidence that PTSD may mediate and possibly moderate the relation between violence exposure and substance abuse, though formal tests of these models have not been conducted. Less is known about physiological arousal as a moderator or mediator of the relationship between violence exposure and substance abuse, though research in this area is promising. The role of gender in these models warrants further investigation.

Both the Kilpatrick and the Velez and Peirce presentations argue strongly for combating risk for substance abuse by reducing exposure to violence of all types as well as treating symptoms of PTSD. When working with patients with substance abuse, it is particularly important to discuss and assess for violence exposure and trauma. As more is known about the role physiological arousal plays in substance abuse, specific recommendations for assessment can be made.

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SYMPOSIUM XIII

NEUROPEPTIDERGIC RESPONSES TO PSYCHOSTIMULANT DRUGS OF ABUSE: STRATEGIES FOR DRUG DEVELOPMENT

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Stimulant-Induced Changes in CRF Peptidergic Systems

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Neuroadaptive changes induced by chronic drug or alcohol use have been implicated in mood dysregulation, anxiety, and increased sensitivity to stress, symptoms that emerge during withdrawal and may motivate continued drug use or contribute to relapse risk during abstinence. An important neuroadaptive mechanism that may underlie these consequences of chronic drug use is dysregulation of non-neuroendocrine, extrahypothalamic corticotropin-releasing factor (CRF) systems in the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST).

CRF neurons in the CeA and BNST play a central role in the regulation of behavioral and emotional responses to stress. A growing body of evidence suggests that these CRF systems also play a significant role in drug-seeking behavior associated with stress and stress-like symptoms that accompany withdrawal from drugs of abuse [1-3]. Extracellular CRF levels in the CeA are substantially elevated during withdrawal from chronic cocaine, ethanol, morphine, and cannabinoid treatments [1]. This CRF hyperactivity is associated with substantial anxiety and stress-like responses as suggested by findings that functional antagonism of extrahypothalamic CRF transmission attenuates these behavioral manifestations of withdrawal in the case of alcohol [4], cocaine [5], and opiates [6]. While there is strong evidence implicating the CeA as an important site mediating behavioral signs of drug and alcohol withdrawal [4, 6, 7], recent findings have implicated CRF neurons in the BNST as well [8].

The data presented above identify hyperactivity of extrahypothalamic CRF systems as a common neurobiological mechanism for anxiogenic and stress-like symptoms that accompany withdrawal from alcohol and drugs of abuse. However, activation of extrahypothalamic CRF neurotransmission may also play a role in reward deficits and "dysphoria" as measured by brain stimulation reward thresholds [9] that are a common consequence of withdrawal from drugs of abuse [10]. Thus, changes in the regulation of the activity of the extrahypothalamic CRF systems may represent a critical neuroadaptive mechanism responsible for the development of dependence and compulsive drug-seeking behavior.

The CRF system in the CeA has a role not only in acute withdrawal, but long-lasting perturbations in this system may underlie increased stress sensitivity, anxiety-like symptoms and heightened drug-seeking behavior during the protracted withdrawal phase. Several recent findings support this hypothesis. First, measures of whole tissue levels of CRF in the amygdala of rats withdrawn from chronic cocaine or ethanol indicate that this peptide system remains dysregulated (> 6 weeks) long after acute withdrawal [11]. Second, protracted ethanol withdrawal was found to be accompanied by increased anxiety and stress reactivity as well as increased ethanol self-administration and these effects persisted for at least six weeks of abstinence [12]. Lastly, all of these withdrawal effects including anxiety, increased ethanol intake, and enhanced susceptibility to stress-induced ethanol-seeking were dose-dependently reversible by ICV administration of the CRF receptor antagonist, D-Phe-CRF [12].

An important question is whether abnormalities in extrahypothalamic CRF function during protracted withdrawal represent a factor in enhanced vulnerability to relapse. Recent work addressing this issue revealed that previously ethanol dependent rats tested three weeks after withdrawal show increased susceptibility to reinstatement of ethanol-seeking behavior induced by footshock stress compared to rats without a history of ethanol dependence [13]. Like the protracted withdrawal symptoms described above, the stress-induced reinstatement of ethanol-seeking was dose-dependently reversible by the CRF receptor antagonist, D-Phe-CRF.

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Overall, these findings implicate dysregulation of the non-neuroendocrine CRF stress systems as a common factor in the anxiogenic and aversive consequences of acute and protracted withdrawal from drugs of abuse. Moreover, the data support the existence of a link between long-lasting abnormalities in CRF function and vulnerability to relapse during protracted abstinence. Finally, it is important to note that CRF antagonists effectively reverse anxiety and stress-like symptoms and attenuate increased drug intake as well as vulnerability to stress-induced relapse without producing significant behavioral effects in non-dependent rats [12-15]. This suggests that these agents do not interfere with normal motivated behavior in nondependent individuals and identifies the extrahypothalamic CRF system as a promising target for the pharmacotherapeutic treatment of acute and protracted withdrawal symptoms and the prevention of relapse.

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NEUROPEPTIDE mRNA RESPONSES TO PSYCHOSTIMULANTS

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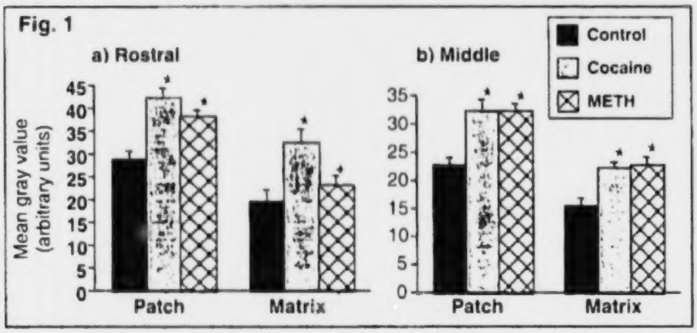
INTRODUCTION: Psychostimulants, such as methamphetamine (METH) and cocaine, exert their acute, and presumably their long-term effects by increasing the extracellular concentrations of monoamines. While this increase in extracellular monoamines is the fundamental initiating step, the post-synaptic impact of this increase is likely critically important for both the acute and long-term impact of psychostimulants.

The dorsal striatum receives extensive dopamine and serotonin innervation. Consequently, striatal efferent neurons are prime targets for psychostimulant-induced changes in extracellular monoamines. Striatonigral ("direct" pathway) neurons co-express the neuropeptides dynorphin, neurotensin, and substance P. Striatopallidal ("indirect" pathway) neurons, on the other hand, co-express met-enkephalin and neurotensin. Given this localization of neuropeptides in striatal efferent pathways, changes in neuropeptide mRNA expression can be used as indices of changes in the function of distinct striatal efferent pathways induced by different stimulants. The present study was therefore designed to directly compare the effects of METH and cocaine on neuropeptide mRNA expression in the dorsal striatum to evaluate the extent to which unique stimulants differentially impact basal ganglia function.

METHODS: Adult, male Sprague-Dawley rats (Simmons Laboratories, ~300 g) were used for all experiments. On the day of the experiments, rats were transferred to plastic tub cages and taken to the laboratory. Approximately 1 hr later, rats were injected with either saline vehicle, cocaine (30 mg/kg, i.p.), or METH (2.0 or 15.0 mg/kg, s.c.). Rats were sacrificed 3 hr after the injection by exposure to CO2, and the brains were removed and rapidly frozen in isopentane chilled on dry ice. Frozen brains were subsequently sectioned into 12-μm coronal sections through the rostrocaudal extent of the striatum. Slide-mounted sections were then processed for *in situ* hybridization histochemistry for detection of preprodynorphin (PPD) and neurotensin/neuromedin N (NT) mRNA expression as previously published (Adams *et al.*, 2000, 2001). In addition, in some cases, adjacent sections were processed for mu-opioid receptor immunoreactivity to define the patch-matrix organization of the striatum.

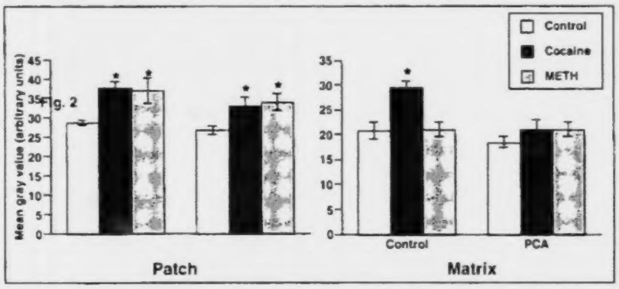
RESULTS: In rostral striatum, METH (15 mg/kg) increased PPD mRNA expression selectively in the patch (striosome) compartment (Fig. 1a). Cocaine (30 mg/kg), on the other hand, increased PPD mRNA expression in both the patch and matrix divisions of rostral striatum (Fig. 1a). In middle and caudal aspects of striatum, both METH and cocaine increased PPD mRNA expression in both the patch and matrix (Fig. 1b). To further evaluate the mechanisms underlying these differential effects of high, equimolar doses of METH and cocaine in rostral striatum, rats were administered a lower, 2.0 mg/kg, dose of METH that was determined by *in vivo* microdialysis to produce an increase in extracellular DA equivalent to that produced by 30 mg/kg cocaine. In this case, cocaine again increased PPD mRNA expression in both the patch and matrix compartments, but METH had no significant effects in any region (data not shown). Thus, doses of METH and cocaine that produce equivalent increases in extracellular DA exert different post-synaptic effects on neuropeptide mRNA expression in the striatum and greater increases in extracellular DA are needed in response to METH in order to affect neuropeptide mRNA expression.

Fig. 1

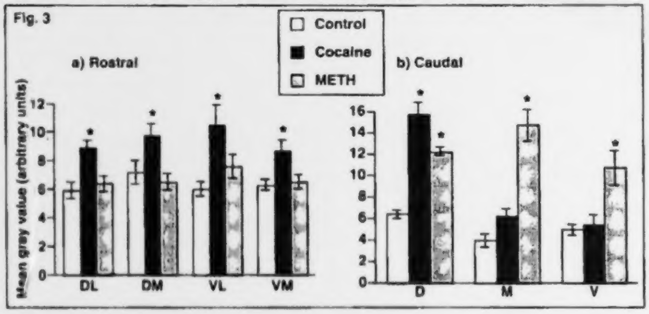


The role of serotonin (5-HT) in the differential effects of the high doses of METH and cocaine also was examined. As before, in control rats, 15 mg/kg METH increased PPD mRNA expression selectively in the patch division of rostral striatum, whereas 30 mg/kg cocaine increased it in both the patch and matrix divisions (Fig. 2). However, in rats with an ~80% loss of striatal 5-HT induced by *p*-chloroamphetamine (PCA; 8.0 mg/kg, i.p.) one week prior to the experiment, cocaine no longer significantly altered PPD mRNA expression in the matrix compartment of rostral striatum (Fig. 2). PCA-induced loss of 5-HT did not alter the effect of METH on PPD mRNA expression in any region of striatum, nor did it alter the effects of cocaine in more caudal striatum. Thus, in rostral striatum induction of PPD mRNA expression in the matrix compartment by cocaine depends on activation of 5-HT receptors.

Fig. 2



High, equimolar doses of cocaine and METH also had differential effects on the expression of NT mRNA expression in rostral and caudal striatum (Fig. 3). In rostral striatum, cocaine, but not METH, significantly elevated NT RNA expression in the dorsolateral (DL), dorsomedial (DM), ventrolateral (VL), and ventromedial (VM) quadrants of dorsal striatum (Fig. 3a). In more caudal regions of striatum, the effects of METH became more apparent in dorsal (D), middle (M), and ventral (V) aspects, and the effects of cocaine became restricted to the dorsal aspect (Fig. 3b). As was the case for PPD mRNA expression, PCA-induced loss of serotonin blocked the effects of cocaine on NT mRNA expression in rostral striatum, but had no effect on the induction by either cocaine or METH in more caudal aspects of striatum (data not shown).



DISCUSSION

The present results reveal that high, equimolar doses of cocaine and METH exert differential effects on PPD mRNA expression in the patch-matrix division of rostral striatum, and also differentially affect PPD and NT mRNA expression in rostral versus caudal striatum. Cocaine induces PPD mRNA expression in both the patch and matrix divisions of rostral striatum, whereas METH induces it only in the patch compartment. Likewise, cocaine has greater effects on NT mRNA expression in rostral striatum, whereas the effects of METH become more apparent caudally. These findings are consistent with experiments previously published by Graybiel and colleagues (Graybiel *et al.*, 1990; Moratalla *et al.*, 1992) showing differential expression of immediate early genes in response to amphetamine and cocaine. Thus, the differential effects of METH and cocaine on neuropeptide mRNA expression likely reflect general differences in the response of striatal efferent neurons in the patch-matrix compartments of rostral striatum and across the rostrocaudal extent of striatum to METH and cocaine. The present data further extend those findings by demonstrating that the effects of cocaine in rostral striatum, particularly in the matrix compartment, are dependent on 5-HT. The effects of METH and cocaine in the rostral patch compartment and in more caudal aspects of striatum, on the other hand, are not sensitive to loss of 5-HT, and therefore are more likely dependent on extracellular dopamine activating D1 dopamine receptors (Spangler *et al.*, 1996; Wang and McGinty, 1996). Given that the relative activation of neurons in the patch-matrix compartment of rostral striatum may be related to the development of stereotypic behavioral responses (Canales and Graybiel, 2000), and the role of serotonergic agents in the management of obsessive-compulsive syndromes, further examination of the role of 5-HT in the neuropeptide response to psychostimulants is warranted.

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LOCAL OPIOID REGULATION OF AMPHETAMINE-INDUCED GENE EXPRESSION IN THE STRIATUM

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Striatal kappa opioid receptor agonists reduce the behavior and gene expression induced by a single dose of amphetamine by decreasing dopaminergic and glutamatergic transmission (Gray *et al.*, 1999; Tzaferis and McGinty 2001). However, less is known about the effects of blocking striatal mu and delta opioid receptors on stimulant-induced behavior and gene expression. Therefore, in this study, the opioid receptor subtype selective antagonists, CTOP (mu), TIPP[psi] (delta), or vehicle were infused into the dorsal striatum 10 minutes before acute systemic administration of amphetamine (2.5 mg/kg, i.p.) or saline. Distance traveled and vertical activity were analyzed as a reflection of locomotor activity and rearing in Accuscan photocell chambers. The rats were anesthetized and decapitated 3 hours after the systemic injection and the brains were processed for semi-quantitative in situ hybridization using ^{35}S-dATP-labeled probes for preproenkephalin (PPE), preprodynorphin (PPD), and substance P (SP) as described (Gonzalez-Nicolini and McGinty 2002). Acute administration of amphetamine increased distance traveled and vertical activity. CTOP (1 μg/μl) and TIPP[psi] (2 μg/μl) both decreased vertical activity without altering distance traveled. TIPP[psi] completely blocked amphetamine-induced increases in PPD, PPE, and SP whereas CTOP significantly decreased amphetamine-induced SP but not PPE mRNA expression. In fact, CTOP alone increased PPE mRNA levels in the dorsal striatum. These data indicate that both mμ and delta selective receptors in the striatum actively regulate amphetamine-induced behavior and gene expression. Mμ receptors are primarily expressed by medium spiny neurons located in the patch compartment of the striatum that project to the substantia nigra pars compacta (Herkenham and Pert 1982; Gerfen). It is possible that blockade of mμ receptors on these neurons leads to a trans-synaptic inhibition of dopamine neurons in the substantia nigra that would reduce the response to amphetamine. In contrast, delta receptors are expressed by striatal, particularly cholinergic, interneurons with a small percentage of receptors located in presynaptic terminals (Svingos *et al.*, 1998). Intra-striatal perfusion of the delta opioid antagonist, naltrindole, decreases amphetamine-evoked extracellular glutamate levels in the striatum (Rawls and McGinty 2000). A direct or possibly an indirect, trans-synaptic mechanism may underlie this effect because delta receptor blockade increases acetylcholine release in the striatum and muscarinic receptor agonists decrease evoked glutamate release in vivo (Rawls and McGinty 1998) and in vitro (Rawls *et al.*, 1999). Thus, the selective distribution of opioid receptors on different cell types in the striatum provides for a synergistic regulation of striatal output at both the pre-synaptic and post-synaptic levels.

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SYMPOSIUM XIV

THE NEW THING: APPLYING INFORMATION TECHNOLOGIES TO DRUG ABUSE PREVENTION AND TREATMENT

W.K. Bickel and A.T. McLellan, Chairpersons

APPLYING COMPUTER TECHNOLOGY TO DRUG ABUSE PREVENTION SCIENCE

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Drug abuse unfortunately remains a major public health problem in the U.S. More disconcerting is the recent evidence that drug abuse is increasing among school-aged children and adolescents. For example, the Monitoring the Future Study funded by the National Institute on Drug Abuse (NIDA) shows that from 1991 to 1999, marijuana use doubled among 8th graders, increased by over 70% among 10th graders and grew by more than 35% among 12th graders. Rates of use of any illicit drug increased by about 50% among 8th and 10th graders and 25% among 12th graders. Particularly startling, heroin use by 12th graders has increased by over 100% since the beginning of this decade (NIDA, 2000; Johnston *et al.*, 1995; Schwartz, 1998).

Drug use during these formative years may produce a number of negative outcomes (e.g., Ellickson, 1995). Drug use at an early age may increase the likelihood of using other drugs, increase risky behavior (e.g., alcohol-related accidents; risky sexual behavior), and lead to poor educational outcomes that may have long lasting negative personal and economic consequences (e.g., not finishing school, delinquency, difficulty in making the transition to adulthood). Additionally, the trend of increased injection drug use by adolescents increases their risk of contracting and spreading hepatitis, HIV and other serious diseases (Deas-Nesmith *et al.*, 1999). Clearly these trends and the consequences possible from the trends emphasize the importance of drug abuse prevention efforts.

Several drug abuse prevention programs, such as the Life Skills Training Program, have had positive effects in reducing drug use behavior (Bauman and Phongsavan, 1999; Botvin, 2000; Hansen 1992). Although such effective programs exist, the applications of primary prevention programs in schools throughout the country, however, lead to several challenges. First, many of the most widely adopted prevention programs, such as Project DARE (Drug Abuse Resistance Education) have been shown to be ineffective (Lynam *et al.*, 1999). Despite its ineffectiveness, DARE has been widely adopted as a prevention effort, probably due to its (1) limited cost to a school, as it is funded by law enforcement agencies, and (2) use of law enforcement personnel to teach material, thereby enabling teachers to avoid spending considerable amounts of time learning and implementing the prevention curriculum. In addition, currently existing programs that are of demonstrated efficacy are challenged by (1) the cost and time to train teachers to implement the programs and (2) the difficulty in insuring the fidelity of the intervention. For example, the negative results reported in one prevention research study were attributed to the faulty implementation of the prevention program by poorly motivated, classroom teachers (Hansen *et al.*, 1988). These challenges in current prevention efforts support the need to develop methods that will insure fidelity of application, require limited teacher support or training and are cost-effective. Indeed, the lack of prevention programs that are simultaneously systematic, efficacious, cost-effective, easily exportable and able to be applied with fidelity demonstrate the need to develop innovative prevention systems which extend beyond traditional educational interventions.

In order to address these challenges, we developed and evaluated a science-based, computerized drug abuse prevention multimedia program for middle school-aged adolescents. The program was developed for 6th, 7th, and 8th grade students and was designed with continual input from focus groups of middle school-aged adolescents. The program's curriculum incorporates the components of drug abuse prevention efforts that have been shown to be effective in preventing initiation to drug use (e.g., drug-refusal skills training, general decision-making skills, social skills training).

The prevention curriculum is presented using both fluency-based Computer-Assisted Instruction (CAI) (© Copyright HealthSim, Inc., 1997) and video-simulation technologies. Fluency-based Computer-Assisted Instruction (CAI) is an educational technology that has been shown to be efficacious in promoting long-term retention of information by requiring learners to respond to questions posed about information they are learning at a pre-determined level of speed and accuracy. This technology thus systematically promotes mastery of information one is learning. The video simulation technologies consist of interactive videos, where the user of the program can choose to watch various interactive video clips where adolescent actors/actresses depict a scene of relevance to a given topic of drug abuse prevention (e.g., drug refusal skills). In this process, the learner can decide what decisions they would like various characters in the video to do and can thus explore the differential consequences of various choices they make in this simulated setting. The program also includes a game that participants can access after completing a certain number of program modules. In the game, the adolescent can assume the identity of a character that enters the game with a pre-set history or disposition (ranging from bad, neutral to good). The adolescent can live a week in the life of this individual and can thus learn about 1) the cumulative effects of making a series of decisions and 2) how certain choices may change the opportunities one encounters (e.g., as one makes more and more risky choices, they may be presented with an increasing number of risk opportunities).

The computerized drug abuse prevention program was developed in accordance with established scientific principles important in preventing drug use among adolescents. Specifically, this program is designed to promote well-known "protective factors" (such as social skills, decision-making skills, and self-efficacy). It is also designed to target all forms of drug use, especially, cigarettes, alcohol, marijuana, but also other illicit drugs. The program also provides training in drug-refusal skills, social competency, and attitudes against drug use, and uses interactive methods rather than lecturing techniques. Additionally, the program content was designed to be age-specific, developmentally appropriate, and culturally sensitive.

This program is designed to promote the increased adoption of effective prevention science, as it is designed to be efficacious, cost-effective, easily deployed, and able to be applied with fidelity. The program is also designed to foster high levels of interaction between the adolescent user of the program and the content of the program itself and to be highly acceptable to students and teachers. The program enables educators to allocate the amount of time that they typically spend in teaching drug abuse prevention principles to their students, to intensive prevention efforts for "at risk" youth instead. Finally, the program can readily and easily accommodate new educational information as it becomes available.

Approximately 60 middle-school aged adolescents (including Caucasian, African American, Hispanic and Cambodian youth) participated in feedback sessions to evaluate the program. Half of these participants were from mostly middle-class settings in Vermont and the other half were from economically disadvantaged areas of Philadelphia. Importantly, the resulting data from these two groups of adolescents did not differ, and thus their data were combined in data analyses. Results indicated that adolescents who evaluated the program reported (on 100 mm Visual Analog Scales) that the computer-based program was highly useful (mean usefulness=73.23; SEM=3.07) and was as useful as their previous school-based drug abuse prevention education (mean=65.03; SEM=3.49). Additionally, participants reported that they learned a great deal about what to do when offered a drug from the computer-based program (mean=75.03; SEM=3.73) and their school-based program (mean=76.10; SEM=3.84). Participants also reported that the computer-based program was highly interesting (mean = 76.01; SEM=2.78) and fun (mean=73.58; SEM=3.25) and rated the computer-program to be significantly more interesting and more fun relative to their school-based drug abuse prevention training (interesting mean=52.75; SEM=4.02; mean fun=48.86; SEM=6.04). When asked how the computer-based program ranked in comparison to their previous drug abuse prevention training (using a scale that ranged from 0-100, where 0 meant "This program is much worse" and 100 meant "This program is much better"), participants rated the computer program as much better than their previous drug abuse prevention education (mean score=75.37; SEM=3.55). Furthermore, participants demonstrated dramatic increases in their percent accuracy on measures assessing knowledge about drug abuse prevention (from approximately 25-50% accuracy at baseline compared to 95-100% accuracy on these knowledge tests after completing the computer-based drug abuse prevention program).

This program is currently being further evaluated in a school-based setting during the 2001-2002 academic year. In this year-long study with four middle schools (and hundreds of middle school-aged youth) in the state of Vermont, we are comparing the efficacy of this computer-based program to the Life Skills Training drug abuse prevention curricula (the "gold standard" of prevention interventions). In this process, we are asking middle school-aged students to complete a battery of standardized assessments both before and after their drug abuse prevention education. Preliminary results demonstrate that middle school aged youth show large increases in their percent accuracy on measures of knowledge about drug abuse prevention and that adolescents who complete the computer-based intervention have significantly higher percent accuracy on these measures compared to those who have completed the Life Skills Training program. Importantly, students report marked decreases in their intentions to use various drugs after having completed the computer-based program compared to their self-reported intentions about drug use before their prevention training. Additionally, teachers reported that they liked the ease of implementation of the computer-based drug abuse prevention program and how use of the computer-based program enabled them to focus more personalized attention on the most high-risk group of adolescents. Moreover, a cost-effectiveness analysis revealed that the cost of employing the computer-based drug abuse prevention program in a school setting (e.g., cost of licensing the program and receiving support) is approximately half the cost of implementing the Life Skills curriculum (e.g., including the cost of teacher training, curriculum content, student workbooks, teacher salary/time to implement).

An effective multimedia drug abuse prevention learning environment, which provides an integration between state-of-the-art computer technology and behavioral science research, may be of substantial benefit in providing drug abuse prevention education to middle school-aged adolescents in a manner that is considerably more cost-effective and comprehensive than the labor-intensive, prevention interventions that have been demonstrated to be efficacious in preventing the initiation of drug use among adolescents. The computer-based drug abuse prevention program used in the school setting would also increase the standardization of science-based approaches to prevent the initiation of drug use among adolescents.

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COMPUTER-ASSISTED ADMISSION ASSESSMENT TREATMENT PLANNING AND SERVICE REFERRAL: EFFECTS ON COUNSELORS AND PATIENTS

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ABSTRACT

This study evaluated the benefits of a brief training and treatment-services matching technology designed to give clinical meaning and value to a research-based assessment, and thereby improve treatment planning and services matching. The study used the Addiction Severity Index (ASI) as the assessment. Data were analyzed from 95 patients of 26 counselors in 8 treatment programs, randomly assigned to one of two conditions. Standard Assessment Training (ST) included a two-day training course on the use of a computer-assisted ASI interview. Enhanced Assessment and Treatment Care Planning Training (ET) also used exactly the same computer-assisted ASI training, but added 2 hours of training on how to use the new technology; a computer Resource Guide (RG) to free or low-cost "wrap-around" (e.g. medical, employment, legal, housing, psychiatric) services. This training was expected to provide the counselors with a concrete method of using the ASI information to develop better treatment plans at admission and to access more comprehensive services for their patients. Both groups were equally likely to complete the ASI training and showed comparable scores on ASI competency measures. Patients in the ET group had substantially better-matched treatment plans (patient problems to plans for treatment), and received significantly increased and better-matched services than patients in the ST group.

INTRODUCTION

Computerization has made it much easier to collect, process, and use information. It is now possible to complete interviews directly on computers and to immediately convert that information into relevant clinical reports (Budman, *et al.*, 2001, Carise *et al.*, 1999; 2000). There have been many developments in the science of patient measurement that could be relevant to the clinical tasks of patient assessment and treatment planning. The Addiction Severity Index (ASI) is an assessment interview that has been developed and used in more than 500 clinical and health services research protocols (McLellan *et al.*, 1985, 1992). Consequently, there is reason to think that if this research-derived, clinical interview could be made more relevant to the clinical tasks of assessment and treatment planning, more cost effective and easier to use by those charged with completing it, it would be better implemented, lead to increased patient engagement, and possibly even better treatment experiences and outcomes. Additionally, "wrap-around" social services have been shown to improve treatment outcomes, but finding these services can be time-consuming and costly for counselors. Computer technology could make a user-friendly resource guide for locating and revering patients to needed services.

PROCEDURES

A Resource Guide (RG) was adapted and expanded for this study, detailing information on agencies providing free or low-cost services in social and personal health areas (e.g. employment, housing, legal, medical, etc) in Philadelphia. The RG was adapted from the Electronic Edition of the First Call for Help directory developed by the United Way of Southeastern Pennsylvania in cooperation with Dorland's Directories (Mackie & Walton 1998). The Guide included information on 1524 agencies, linked by agency name, services provided, and 131 keywords. The resource guide, sorted by problem area, included substantial descriptive information about each agency (programs, special services available, fee structure, eligibility, etc.) and all necessary contact information to facilitate easy needs-services matching. Nine treatment programs were originally randomly assigned and participated, however, there was an outlier in the ET group that provided such an unusually high number of services and service referrals, that we excluded this program from the analysis. Treatment programs were offered $200 for each participating counselor (up to a maximum of $1,000) to cover the costs of lost staff time while participating in research data collection. The counselors within these programs received $75 for their participation as well as the continuing education credits. Both counselors and patients provided written informed consent. Counselors at each site were free to decline participation and were assured that their employment would not be affected in any way by participation or non-participation.

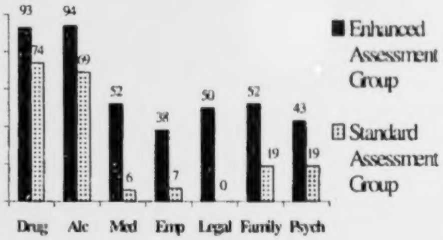
Counselors in both conditions (ST and ET) were provided with manuals, ongoing access to a toll-free help line, post training competency feedback, and a 12-hour training on administering the ASI using an ASI software program originally developed for a national project - the Drug Evaluation Network System (DENS) (Carise, et. al, 1999). This ASI training also included use of report generating software functions, including a narrative summary of the ASI information on each patient. The ASI provides measures of the nature and severity of problems in medical, employment, alcohol/drug use, legal status, family relations and social support and psychiatric function. The reliability and validity of the instrument has been found to be high across a wide range of substance abusers (McLellan *et al.*, 1985, 1992). Counselors in the ET condition also received an additional 2-hours of hands-on training in using the RG software to find social and personal health services for their patients and to integrate this information in treatment planning. Counselors recruited patients at the time of intake. Patients were told that the research project would not interfere with their treatment and that all information would be kept confidential from all persons and agencies.

Patients were contacted by researchers from the Treatment Research Institute for brief, confidential interviews at two and four weeks following their admission. Patients were offered $10.00 for each of the two 15-minute telephone interviews. We used the Treatment Services Review (TSR) (McLellan, *et al.*, 1992a; 1992b; 1993) in these interviews to measure the nature and amount of services actually received by the patients. The TSR is a brief (10-15 minute), structured interview administered in person or over the phone to the patient. The TSR was designed to provide information on the type, amount and efficacy of services provided (directly or indirectly) to a substance abuse patient while in treatment. The TSR has been shown to provide a reliable and valid record of the number and types of services received, both in and out of the treatment program. All patients approached by counselors agreed to participate. In summary, all data reported here result from 8 programs, 26 counselors and 95 patients who participated in the study.

RESULTS

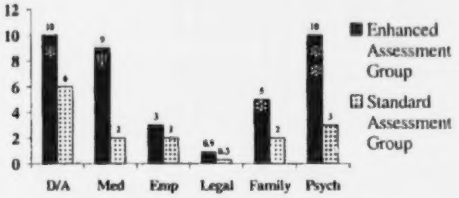
There were no significant differences between treatment programs in the two groups (ST and ET) on measures of organizational, patient, or services profiles, financing or staffing mix. There were no differences between counselors in the 2 groups on prior ASI training, years of education, or "recovery status". Standard competency measures were collected from all counselors to test understanding of the ASI (Fureman *et. al*, 1994). There were no significant between-groups differences in competency as measured. Counselors in the ST averaged 69% and counselors in the ET group averaged 77% (F=2.139, df=(1,32), p=.16). Additionally, there were no significant between-groups differences between counselor competencies as measured by a standardized video coding exercise. (ST=82%, ET=87%, F=2.181, df=(1,22), p=.16). These scores are considered acceptable evidence of counselor competency in understanding and using the ASI. There were no between groups differences in overall measures of patient's problem acuity based on ASI composite scores, however, patients in the ST group were younger (ST=36, ET=41, p<.05), more likely to be female (ST=53%, ET=24%, p<.005), and more likely to be African American (ST=84%, ET=75%, p<.05).

Hypothesis 1: Counselors trained in the Resource Guide will develop Treatment Care Plans that are better matched to patients' needs. For those patients who needed services based on ASI data, patients in the ET group were significantly more likely to have this need addressed in their treatment care plan than patients in the ST group. This is seen in every domain of the ASI – Medical and Employment (both p<.001), and Alcohol, Drug, Family, Legal, and Psychiatric domains (all p<.05).


% Matched: ASI to TCP

Hypothesis 2: Patients of counselors trained on the Resource Guide will receive more services, and services that are better matched to their needs. In the first 2 weeks of treatment, patients in the ET group received significantly more Psychiatric services (ST=3, ET=10, p<.001), Family services (ST=2, ET=5, p<.05), Medical services (ST=2, ET=9, p<.05), and drug/alcohol services (ST=6, ET=10, p<.05). There were no significant differences in employment and legal services. Additionally, patients in the ET group were more likely to receive services that were matched to their needs based on ASI assessments in 3 of the ASI domains – Alcohol, Legal, and Psychiatric (p<.05). There were no differences in the other ASI domains.

Number of Services Received first 2 weeks



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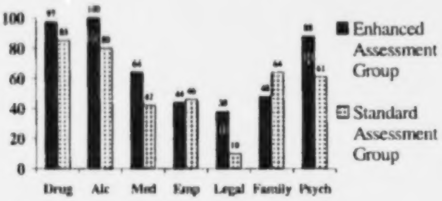
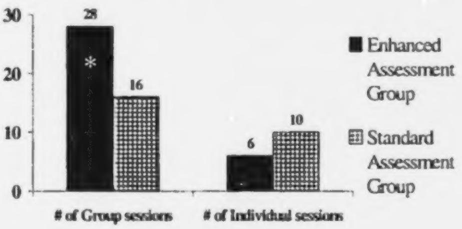
Services received in first 2 weeks



Hypothesis 3: Patients of counselors trained on the Resource Guide will have greater session attendanceand higher program completion rates. Patients in the ET group attended an average of 28 group sessions, whereas patients in the ST group attended an average of 16 sessions (p<.05). Patients in the ST group attended more individual sessions, however, this difference was not significant.

Number of sessions attended (program records)



It should be noted that this study has a number of limitations; it evaluated the type and number of services but not the quality of services received. No pre-study measures of counselor behavior or post treatmentpatient outcomes were included, these are included in a planned Phase II study, and the study was limited to Philadelphia area treatment programs.

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The scientific study of drug dependence has rapidly embraced the advances in neuroscience and genetics. However, it has only recently begun to embrace advances in information technologies. The application of information technologies to prevention and treatment provides unique opportunities to provide, improve, monitor and export cost-effective interventions. The purpose of this symposium is to review recent research that explores a broad range of applications of information technologies to drug abuse prevention and treatment. Specifically, investigators will report on research where (1) a primary prevention program in schools was administered via computer and compared to school personnel administering their usual prevention program, (2) information technologies to assist counselors in treatment planning and service referrals were examined, and (3) a clinical trial was conducted comparing computer delivered and therapist provided treatment to heroin-dependent patients in a buprenorphine clinic.

COMPUTER PROVIDED TREATMENT FOR HEROIN DEPENDENCE: A CONTROLLED STUDY

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Although several behavioral therapies have documented efficacy in the treatment of drug dependence, challenges to their adoption exist. For example, staff may be resistant to changing their therapeutic approach. Moreover, the training of staff is both expensive and time consuming and, once staff are trained, ensuring the fidelity of the intervention poses additional challenges. For these and likely other reasons, diffusion of innovation may be slower than may be preferred. For these reasons, we were interested in examining treatment provided via computer.

There are 8 potential benefits of providing computer-based treatment: First, it can be provided at a lower cost than therapist-provided treatment. Second, computer-based treatment is easily exportable. Third, when exported, the fidelity of such program is assured. Fourth, computerized treatment may be less threatening than therapists when addressing sensitive topics such as sexuality or substance use. Fifth, appropriately designed, computer programs require patients to continuously demonstrate the knowledge they have acquired. Sixth, computerized treatment can be easily modified to accommodate new research findings. Seventh, such treatment can be available at the patients' convenience. Eighth, computerized treatment may permit more rapid diffusion of evidenced-based treatments. Potential disadvantages of computer-based treatment includes 1) it cannot provide outreach, 2) if therapeutic alliance is important to treatment effectiveness, then the impact of computer-based treatment on therapeutic alliance is unknown, and 3) the acceptability of such treatments to the patients is also unknown.

Prior research on computer provided therapy has generally demonstrated that computer- and therapist-provided treatments produce comparable results. The most extensively investigated area in computer-delivered therapy has been the cognitive-behavioral treatment of anxiety and depression. For example, Selmi et. al. (1990) compared a treatment delivered by a computer or by a therapist with a waiting list control in depressed patients. The two active treatments were found not be different from each other, but both produced significantly better results than the control group. Similarly, Newman *et al.*, (1997) found comparable treatment effects for panic disorder between therapist-delivered, and combined therapist-computer delivered treatment, but demonstrated that the combined treatment is less costly. In the area of substance abuse, there is a more limited literature. One well-conducted study compared heavy drinkers who received computer treatment to those in a wait list control (Hester & Delaney, 1997). Heavy drinkers who received the computer program showed greater improvement than a waiting list control group, and the waiting list control group later received the computer based treatment and showed similar improvement.

In order to empirically examine the potential advantages and disadvantages of computer-based treatment, we designed and are in the process of conducting a random-assignment, controlled clinical trial in the context of a research clinic for opioid-dependent individuals. Patients are randomly assigned to one of three treatments. The first treatment is the Community Reinforcement Approach with vouchers for cocaine and opioid-free urine samples delivered by therapists (Budney & Higgins, 1998). The second treatment is identical to the first treatment but delivered via the computer. The third treatment, referred to as standard treatment, is a control treatment and consists of the treatment typically found in methadone treatment (Ball & Ross, 1991).

The computerized treatment system is interfaced with a semi quantitative urinalysis (UA) machine. The computer program updates voucher earnings dependent on UA results. Therapists and patients can customize the treatment program. Patients complete evidence-based programs modules on skills training, role-playing, exercises and homework in accordance with their plan. The treatment program consists of approximately 50 discrete interactive modules. Some modules use video to teach skills and many modules use the fluency based computer instruction technology described in the preceding paper by Marsch & Bickel (© Copyright HealthSim, Inc., 1997). Electronic reports of patient's activity and UA results are regularly sent to therapists.

To date, 80 opioid dependent individuals have participated in this study. Approximately 25% of these individuals are also cocaine dependent. During the 12 weeks of treatment, standard treatment resulted in approximately 35% opioid free urine samples; the therapist treatment resulted in 56% opioid free urine samples; and the computerized treatment resulted in 50% opioid free urine samples. The cost of these treatments was approximately $20,000 for the standard treatment, $60,000 for the therapist treatment, and $16,500 for the computer delivered. There are no differences between groups on retention, on the ASI drug composite sale, or therapeutic alliance.

Our preliminary results suggest that computer-assisted therapy is generally as effective as comparable therapist-delivered therapy. The computer-based intervention greatly decreases the cost of treatment via reduced patient-therapist contact time. This system could be employed such that therapists focus on aspects of treatment that they are uniquely skilled to address and enables a treatment clinic to potentially see a larger number of patients. Lastly, this approach may help spur the diffusion of science-based treatments into community settings.

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SYMPOSIUM XV

FRENCH EXPERIENCE WITH BUPRENORPHINE

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CLINICAL DATA ON BUPRENORPHINE USE IN FRANCE

Background: Historical Overview to Opioid Dependence Treatment in France

In order to understand the impact of buprenorphine's availability in France, it is useful to review the state of opioid dependence and its treatment in France for the pre-buprenorphine era (Auriacombe 2000). In the late 1980s and early 1990s the population of France was approximately 59,000,000 persons, and there were an estimated 150,000–300,000 problem heroin users (i.e., between 2.5 and 5.1 persons per 1000). In this population of mainly IV users, it was estimated that 30% or more of these persons were HIV positive, and 60% were hepatitis C positive. The primary treatment modality available was specialized clinics that saw approximately 40,000 patients per year, and pharmacological services were extremely limited – there were only two centers at which methadone could be prescribed, and there was only approximately 100 patients treated with methadone at that time. General Practitioners were actively discouraged from treating illegal drug users, and did not use office-based substitution treatments such as methadone or buprenorphine.

In the late 1980s investigational use of buprenorphine treatment for opioid dependence was launched in France. In 1986, selected regions began using buprenorphine for opioid dependence on a limited basis, and French experience with buprenorphine was first reported at the 1992 annual meeting of CPDD (Auriacombe *et al.*, 1992). However, the primary form of treatment in France for opioid dependence was non-pharmacological services provided in special clinics, with extremely limited availability of substitution therapy.

France Approves Buprenorphine for Treatment of Opioid Dependence

In 1995 the French Medication Agency approved buprenorphine for opioid dependence treatment, and marketing of the product began in February 1996 (Tignol *et al.*, 1998). At this point in time the population of France had increased to approximately 60,000,000 persons, and estimates of the extent of problem heroin users had become more precise – in the mid-1990s it was determined there was approximately 150,000–200,000 persons with problematic use of opioids (i.e., between 2.5 and 3.3 persons per 1000). Of these persons, it was now estimated that 10% were HIV positive, and 75% were hepatitis C positive. The number of patients in treatment in specialized substance abuse clinics had increased from 40,000 to 50,000, and the number of patients in methadone treatment clinics had markedly increased – to 6,000 per year – although this was still a low number of patients given the extent of opioid abuse in France.

The use of buprenorphine in France quickly increased. In part, this was related to use by General Practitioners, who were now encouraged to treat opioid dependence in the office setting. By the late 1990s, it was estimated that General Practitioners were treating approximately 65,000 patients per year with buprenorphine, and another 4,000 patients with methadone. By March of 2001, it was estimated that 74,300 patients were being treated with buprenorphine (assuming a sublingual dose of 8 mg/day), and another 9,600 patients were being treated with methadone (assuming an oral dose of 65 mg/day). [It is important to note these estimates are derived by determining the total amount of each medication that has been consumed throughout France, assuming an average daily dose for each medication, then dividing the total amount of each medication by the average daily dose for each to produce an estimated number of patients.]

French regulation of buprenorphine treatment partially explains the extensive use of this medication (Auriacombe 2000) (Tignol *et al.*, 1998). Any physician can begin prescribing buprenorphine, and any pharmacy can provide the medication. There is no requirement of any form of specialized training that must occur before the physician can begin prescribing buprenorphine. The maximum duration of prescribed buprenorphine is 28 days, and the maximum number of take home doses is 7 days worth, although the physician can override this rule and specify more than 7 days be provided to a patient. It is possible for pharmacies to provide daily, supervised dosing with buprenorphine, if specified by the physician. Only the monotherapy product is available (i.e., the buprenorphine/naloxone combination product is not available in France), and sublingual tablets come in three sizes (0.4, 2, and 8 mg).

Methadone treatment's availability is very different (Auriacombe *et al.*, 1994). Only physicians working in state approved substance abuse clinics can begin a patient on methadone, and methadone is initially dispensed on site. Urine testing is compulsory. Once the initial prescriber determines the patient is stabilized, clinical management of the patient and methadone prescription may be transferred to any medical doctor. At that point, dispensing may be done from any pharmacy. Funding and reimbursement is then the same as for buprenorphine.

In addition to the relative ease physicians have in prescribing buprenorphine, reimbursement for services and payment for medication are other factors that are likely to contribute to the frequent use of buprenorphine in France, as described in the next section.

Funding for Substance Abuse and Other Medical Treatments in France

The funding and reimbursement operations in the French health care system encourage the treatment of opioid dependence with buprenorphine. In general, the French Social Security system provides universal medical insurance through a fund that receives contributions from unions, industry, and the government (Fielding and Lancry 1993). A General Practitioner is reimbursed 65% for a patient visit regardless of the length of time that the visit takes –this is approximately $20US for a routine office visit. However, if the patient has a chronic illness, then reimbursement is 100% for an office visit, and payment is directly from Social Security (rather than a fee collected from the patient). Similarly, payment for prescribed medications is reimbursed at 40-60% of cost, although coverage for medications increases to 100% if the patient has a chronic illness. Notably, opioid dependence can qualify as a chronic illness in the French health care system, so payment for office visits (for a person with opioid dependence) and medications (e.g., buprenorphine) can be fully covered by Social Security.

In addition to treatment by General Practitioners, patients with opioid dependence can also be treated in special substance abuse treatment clinics. Funding for this system if provided by the government, and expenses for treatment (both counseling and medications – such as methadone) are completely covered by these governmental funds. There is no charge to the patient for treatment. Thus, medical insurance and funding in France provide minimal barriers to the person seeking substance abuse treatment.

Information About Patients Treated with Buprenorphine in France

An evaluation derived from the French medical insurance database provides useful information about buprenorphine treated patients. A cross sectional study was conducted in January through June of 1999 in the southwest region of France (Damon *et al.*, 2002), an area with a total population of approximately 3,000,000. A total of 2454 patients were identified – 2341 had been treated with buprenorphine (average dose, 9 mg/day), 102 patients had been treated with methadone (average dose, 73 mg/day), and 11 patients had been treated with buprenorphine and methadone during this time period (i.e., on one, than the other medication at some point). 72% of patients were male, with an average age of 32 years, and 59% of patients had another prescription (of which 90% of these were for benzodiazepines, and the other 10% were for antidepressants). The overwhelming majority of patients saw General Practitioners (96%), although only 20% of General Practitioners in this region prescribed buprenorphine medication. It was quite unusual for General Practitioners to see large numbers of buprenorphine-maintained patients; 0.8% of the General Practitioners had more than 50 buprenorphine-maintained patients, and 84% of the General Practitioners had 5 or fewer buprenorphine-maintained patients. Among the pharmacies in this region, 80% had filled a buprenorphine prescription at some point in time. Similar findings have been reported for other regions of France (Thirion *et al.*, 2002) (Vignau *et al.*, 2001).

Efficacy and Safety of Buprenorphine

Numerous controlled clinical trials have examined the efficacy of buprenorphine, especially compared to methadone, and these studies will not be reviewed here. Since 1993, the French government has been sponsoring the Bordeaux-Bayonne Buprenorphine/Methadone Treatment Research System, an examination in the naturalistic environment of buprenorphine and methadone treatment safety and efficacy. In the beginning of this project, an initial feasibility study examined 12-month outcomes for patients treated in the office setting with buprenorphine

(Auriacombe *et al.*, 1999). Urine samples were collected weekly for toxicology testing, and abstinence was defined as ≤1 opioid positive sample per month. Results from this feasibility study showed that nearly 100% of patients had an opioid positive urine sample at baseline, and that more than 90% of patients had achieved abstinence by the 12-month follow-up.

Within the French treatment system, an important variable that may influence office-based treatment efficacy could be the frequency with which supervised doses of buprenorphine are administered. In a recent study examining this, 202 patients were assigned quasi randomly to daily supervised dosing for either 6 months, 3 months or two weeks after which dosing was on a weekly schedule (Auriacombe *et al.*, 2002). Results from this study showed that retention in treatment at six month follow up was highest for those patients in the 6 month daily supervised dosing group (80%), lowest for those patients in the two weeks daily supervised dosing group (46%), while the 3 month daily supervised dosing group fell between these two (65% retained at 6 months). Rates of opioid positive urine samples were lowest for the 6-month daily-supervised dosing group (14%) compared to the 3 month daily supervised (22%) and two weeks daily supervised (18%) groups. Finally, average daily doses at the six-month assessment were similar for the three groups (7.9, 8.7, and 8.5 mg/day for the 6 months, 3 months or two weeks groups, respectively). These results suggest that initial efficacy for office based buprenorphine treatment may be enhanced by a more closely supervised delivery of medication.

Turning to the safety of buprenorphine, it should first be noted that this topic is addressed in detail in sections below. However, some information about side effects of buprenorphine compared to methadone is available from the French Bordeaux-Bayonne Buprenorphine/Methadone Treatment Research System. Patients treated with buprenorphine appear to experience fewer side effects than those treated with methadone. A preliminary study compared 29 methadone maintained patients with 22 buprenorphine maintained patients (Dubernet 2002). The former were 70% males, had an average age of 34 years and had been on methadone for an average of 30 months with a mean dose of 126 mg/day. The buprenorphine group consisted of 80% males with an average age of 36 years, and had been treated an average of 52 months with a mean dose of 9.5 mg/day of buprenorphine. The methadone patients reported 23 different side effects (with an average of 12 side effects per patient), compared to 19 for the buprenorphine patients (with an average of 11 side effects per patient). For the methadone group, there were six side effects than occurred in more than 50% of patients (constipation, insomnia, reduced sexual desire, increased weight, sweating, and dental problems). In contrast, there were no side effects that occurred in more than 50% of the buprenorphine patients – three occurred in more than 40% of patients (dry mouth, sweating, and bone and joint pain).

Summary of Background

Prior to the introduction in France of buprenorphine for the treatment of opioid dependence, there were an extremely small number of patients treated with opioid agonist medications but an extremely large number of persons in need of such treatment. The extensive use of buprenorphine over the last six years can be understood as resulting from this large unmet need for such a treatment, as well as a regulatory environment which made it quite easy for physicians to prescribe this medication, and a reimbursement system that provided minimal obstructions for patients to obtain buprenorphine. The result has been a marked shift of patients into treatment, primarily by General Practitioners who generally treat small numbers of patients. Evidence from the experience in France suggests buprenorphine is effective in decreasing illicit opioid use, and has a favorable side effect profile. Subsequent sections of this paper provide a further review of the abuse and safety of this medication.

EPIDEMIOLOGICAL STUDIES OF DIVERTED USE OF BUPRENORPHINE IN FRANCE

Background on Buprenorphine Abuse in France

As was reviewed in more detail above, the French treatment system for opioid dependence underwent a significant change in 1996, with the availability of office based buprenorphine treatment. This system allowed all General Practitioners to prescribe buprenorphine, and non-pharmacological and other services ("global medical, social and psychological therapy") were encouraged but not mandated as part of this treatment. Physicians could prescribe buprenorphine with no specific training in addiction treatment required, although they were encouraged to share their knowledge and experience with others (including pharmacists and the substance abuse treatment center system). Current prescription recommendations note there is a risk of fatal respiratory depression when buprenorphine is used with benzodiazepines, and recommend a maximum daily dose of 16 mg. Within two years of buprenorphine's availability in France, case reports of fatalities among patients receiving buprenorphine appeared in the literature (Reynaud *et al.*, 1998) (Tracqui *et al.*, 1998), and on-going evaluations have been monitoring buprenorphine abuse.

Mechanisms Used in France to Collect Information about Diversion of Buprenorphine

Some characteristics of the French ambulatory health system make it difficult to evaluate buprenorphine use. For example, the system is primarily private; physicians are self-employed. Patients can consult several different physicians and receive prescriptions that are reimbursed by Social Security, without attracting attention. Reimbursement for treatment is relatively straightforward, but there is little review of reimbursement patterns and little data about treatment or prescribing patterns available from Social Security. Finally, physicians are variably cooperative in epidemiologic studies of treatment.

This paper will describe three mechanisms that are available to monitor diversion and abuse of medications in general, and buprenorphine diversion and abuse specifically. One data source is the French health reimbursement system, which can provide information about rates of prescribing and use of particular medications. Since buprenorphine prescriptions are transmitted to the French Social Security system for reimbursement, this electronic database provides a nearly exhaustive and objective source of data on buprenorphine use. However, a limitation of this system is that prescribing data for a medication does not necessarily equate to consumption of the medication (i.e., medication may be lost or diverted and used by different routes, and this system has no information about such events) (Cholley and Weill 1999) (Thirion *et al.*, 2002).

A second mechanism for studying buprenorphine diversion and abuse is surveys of General Practitioners and their prescribing practices and patient characteristics. A limitation to these studies is whether or not the sample of physicians surveyed adequately represents the full population of physicians. However, such systems can provide detection of events at the source, and can provide useful information that is derived directly from clinician experience.

Finally, the Centers for Evaluation and Information on Pharmacodependence (the CEIP programs) provide an important source of information about abuse and diversion of medications. The CEIPS are financed by the federal governmental drug agency, AFSSAPS, and consist of ten centers that collect information about drug diversion and abuse, and provide a number of different surveys and reports that will be described in more detail below.

What is known about Diversion and Abuse of Buprenorphine in France

Results from the French Social Security system show that 95% of prescribers for buprenorphine are General Practitioners, and that 20% of all General Practitioners have prescribed buprenorphine at some point. The mean daily dose of buprenorphine is about 10 mg/day, although there is considerable range in the doses used. Sixty percent of patients are in regular follow up treatment (that is, they have one physician provider and their daily dose level conforms to recommended dosing). Twenty percent of patients use high doses of buprenorphine, which they obtain from multiple physicians. Finally, the other 20% use buprenorphine on an occasional basis. In the year 1999, buprenorphine was the fourteenth most reimbursed medication in France, and in the next year (2000) it had become the eighth most reimbursed medication in the French health care system – the cost of buprenorphine was approximately $80,000,000 in the US in 2000.

The Centers for Evaluation and Information on Pharmacodependence programs (CEIPs) provide several different analyses of drug diversion and abuse, and results from four CEIP surveys will be presented here.

The first is the NOTS system, which is a permanent register of serious drug abuse or dependence cases that have been spontaneously reported by health care professionals. French physicians are legally required to report serious drug abuse/dependence cases to the CEIP/NOTS system. In the year 2001, there were 4277 notifications of abuse or dependence on a drug, but only a small number of these (35) were for buprenorphine. It is believed that this is an underestimate of the number of cases of buprenorphine abuse/dependence, but the reason for such a low rate of spontaneous reporting by health care professionals is not clear.

A second CEIP related survey is the OSIAP, which is an assessment of falsified drug prescriptions (Llau *et al.*, 2002) (Baumevieille *et al.*, 1997). This includes stolen prescription forms, forged prescriptions, altered prescriptions, or any other form of abnormal prescription. In 2001, OSIAP assessed eight community pharmacy networks, and these networks represented approximately 1200 pharmacies (about 5% of all pharmacies in France). In the year 2001, these pharmacies reported receiving 437 falsified prescriptions. Of these, only 39 (8.9%) were for buprenorphine. This low rate of falsified buprenorphine prescriptions may reflect, in part, the relative ease with which opioid dependent persons can access treatment and buprenorphine in France.

The third assessment conducted by CEIP is the DRAMES (Deaths Related to Drug and Substance Abuse). This program monitors deaths in persons who are drug abusers (i.e., the death may or may not be related to the drug of abuse). It attempts to identify the substances involved in a drug abuser death (through autopsy and toxicological testing of body fluids, when available). In the year 2000, 154 drug abuse related deaths were studied. Of these cases, 23 (14.9%) persons had buprenorphine in their system at the time of death, and 19 of these 23 persons (82.6%) had benzodiazepines in their system as well. The association of buprenorphine with benzodiazepines in overdose deaths had been noted and reported by others, and is particularly worrisome in France, where a high rate of benzodiazepine prescribing occurs for all patients (not just those with a substance abuse disorder). (This high rate of benzodiazepine prescribing has been noted for several years – see, for example, the Report of the International Narcotics Control Board for 1999, available at: http://www.incb.org/e/ind_ar.htm.)

Finally, the last system utilized by the CEIP programs to assess drug diversion and abuse is OPPIDUM (the Observation of Illegal Drugs and Misuse of Psychotropic Medications). This is an annual national survey conduced since 1995 that assesses patients seen in treatment and evaluation centers, such as methadone clinics and hospital units for the treatment of substance abuse disorders (Thirion *et al.*, 2001). OPPIDUM evaluates the types of psychoactive substances that patients report ingesting at the time of evaluation and/or treatment entry. In the year 2001 it assessed 2800 patients from 73 centers. Results from OPPIDUM provide information about a sample of persons who received buprenorphine while in treatment (n=1148) compared to a group who received buprenorphine outside of treatment (n=127). The latter tended to be younger (28.4 versus 30.8 years), and more likely to live in poverty (17% versus 8%). Only 1% of patients in treatment had obtained buprenorphine illicitly, while 61% of patients out of treatment had done so. Persons out of treatment also had more cocaine use (15% versus 5%), more intravenous drug use (27% versus 15%), and ingested a higher mean daily dose of buprenorphine (10.7 versus 7.7 mg).

Results from the OPPIDUM program show the most common psychotropic drug class used by buprenorphine maintained persons was benzodiazepines – 33% of buprenorphine patients out of treatment used benzodiazepines, and even 21% of buprenorphine patients in treatment took benzodiazepines. The most common benzodiazepine used was flunitrazepam, and the mean dose used was 8 mg. (The therapeutic dose of flunitrazepam is 1 mg.) Other benzodiazepines used were bromazepam, clorazepate, alprazolam, and diazepam. Finally, while substantial rates of benzodiazepine use were found, it is worth noting that 13% of buprenorphine patients (both in treatment and out of treatment) also were alcohol dependent.

Summary of Epidemiologic Studies of Diverted Use of Buprenorphine

The primary sources of information about buprenorphine diversion and abuse in France are the Social Security reimbursement database and assessments conducted by the CEIP system (especially the OPPIDUM survey). While both systems have detected buprenorphine abuse and diversion, both systems have limitations that may diminish their accuracy. Appropriate cohort studies, including comparisons between French methadone and buprenorphine patients, would be a valuable contribution to the scientific literature and clinical care.

While some diversion and abuse of buprenorphine in France has occurred, this should be balanced by the benefits that have been derived from the availability of buprenorphine. These benefits include the mainstreaming of addiction care into office based medical care, the better medical and social care provided to persons with drug abuse disorders, a marked decrease in heroin use (an OPPIDUM survey found 74% of subjects reported heroin use in 1995, compared to 8% of subjects reporting heroin use in 2000), and a marked decrease in overdose deaths (from 564 in 1994 to 120 in 2000). These reductions in morbidity and mortality, which coincide with the availability of buprenorphine treatment, provide strong and persuasive evidence of the benefits to the French approach for opioid dependence treatment.

BUPRENORPHINE: TOXIC AND ADVERSE EFFECTS

Background

Toxic and adverse effects of buprenorphine can be conceptualized as falling into three general categories: consequences of injecting a drug, such as acquiring an infection (an indirect effect of buprenorphine misuse), hepatitis (i.e., liver damage directly related to buprenorphine use), and fatalities (e.g., related to buprenorphine overdose). Reports on any of these events may be collected from a variety of sources, as described above, including spontaneous reports, post-marketing surveillance programs (such as those conducted by the CEIPs or the drug company), and reports by physicians, pharmacists, and forensic investigators. Following buprenorphine's 1995 approval for opioid dependence treatment, French authorities issued a warning of buprenorphine misuse (1997), and a warning of 31 fatalities associated with buprenorphine use (30 which occurred when buprenorphine was combined with a benzodiazepines; issued in 1998). A third warning was released in 2000, when 53 cases of toxic hepatitis associated with buprenorphine use were identified.

While toxic and adverse events associated with buprenorphine use have been reported, it is important to note that adverse reactions associated with buprenorphine use have been exceedingly rare. In the year 2001, the French Centers for Evaluation on Pharmacovigilance (CRPV) reported there were 18,500 adverse drug reactions for all medications used in France that year. Excluding reports of adverse drug reactions for the low dose form of buprenorphine (i.e., 0.2-0.3 mg), which is marketed for analgesic purposes, there were 849 reports of adverse events related to buprenorphine for the period of 1995-2002 (i.e., an average of approximately 130 events per year, or less than 1% of all reports of adverse drug events in 2001).

Complications Associated with Use Buprenorphine

Parenteral use of buprenorphine has been associated with several somatic complications. The first of these is abscesses, which is a common complication of any intravenous drug abuse. The second complication that has been noted is optic neuritis secondary to infection with Candida albicans. This is an infrequent complication of buprenorphine abuse, and cases have occurred in both HIV positive and negative patients. Other infectious diseases have been reported as associated with parenteral buprenorphine abuse, such as HIV infection and infectious hepatitis. Rare reports of arterial ischemia have occurred when abusers have inadvertently injected buprenorphine into an artery rather than the intended vein. Finally, reports of respiratory depression have been associated with parenteral use of buprenorphine.

Hepatitis has been reported as resulting from buprenorphine use, although such occurs very rarely and appears to be more likely if buprenorphine is used by the parenteral route rather than sublingually (Berson *et al.*, 2001b). 53 cases of cytolytic hepatitis associated with buprenorphine have been reported in France. This appears to be a dose-dependent toxicity that is more likely to occur if the patient has hepatitis C and/or is treated with other medications metabolized by the liver. (For example, since buprenorphine is metabolized by P450 3A4, the P450 3A4 inhibitor ketoconazole should increase buprenorphine blood levels – and thus increase the risk of buprenorphine hepatotoxicity.) Buprenorphine has been shown to produce a mitochondrial hepatocellular toxicity in rat and mouse liver cells, and interestingly, this toxicity appears to be limited to the parent compound (buprenorphine) and is not produced by the metabolic product norbuprenorphine (Berson *et al.*, 2001a).

Other complications associated with buprenorphine-included reports of neonatal withdrawal syndrome in children born to mothers maintained on buprenorphine, and children accidentally ingesting buprenorphine. In the first case, neonatal withdrawal, when observed, has been mild in intensity. It can be treated with opioids if it is of sufficient severity. Cases of accidental ingestion by children have been rare, and the primary effect noted has been sleepiness. There have been no reported fatalities in France of children who have inadvertently taken buprenorphine.

Fatalities Among Patients Maintained on Buprenorphine

There have been a total of 124 cases of French patients who have died while taking buprenorphine (an average of 21 cases per year). In a few cases, it is known the person had ingested buprenorphine for the first time when death occurred. In 6 of these 124, it was determined (e.g., based on interviews with family members) that suicide was the motivation for the death. For those 6 cases, buprenorphine blood levels ranged between 0.9 and 3,276 ng/ml. The remaining 118 deaths do not include cases where another cause of death could be determined (e.g., a fatal car crash

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for a patient maintained on buprenorphine), although not all of these 118 cases had autopsies (so other causes of death cannot be excluded).

A review of the forensic examinations of these 124 cases showed that persons had evidence of injecting drug use (e.g., venous needle scars), signs of asphyxia (such as cyanosis, visceral congestion, and pulmonary edema), and aspiration of gastric contents. However, no other pathologies were found on examination.

Plasma levels of buprenorphine and norbuprenorphine were available for 105 of the fatalities. A therapeutic plasma level of buprenorphine is generally in the 2-10 ng/ml range. For these fatality cases (excluding the 6 suicide cases), buprenorphine plasma levels ranged between 0.1–243 ng/ml, with a mean level of 14.4 ng/ml. Norbuprenorphine plasma levels were between 0.1–65 ng/ml (with a mean level of 9.5 ng/ml), although there were some cases in which norbuprenorphine was not detected – suggesting the person had ingested buprenorphine for the first time at the occurrence of death (Kintz 2002).

Analyses of hair and other body fluids were conducted in some cases. For example, in 37 fatality cases, 33 persons (89%) had buprenorphine detected in their hair (Kintz 2002). This suggests the majority of these patients were ingesting buprenorphine on a chronic basis. Buprenorphine was also found in brain tissue, although the value of assessing buprenorphine levels in the central nervous system of fatality cases is not certain (Tracqui *et al.*, 1998).

Evidence of other drug use was frequently found in these fatalities, and the most common of these was benzodiazepines. 70% of fatalities had evidence of concurrent benzodiazepine use (either alone or with another drug besides buprenorphine). Among buprenorphine treated patients in France, the rate of benzodiazepine use is 19%. Twenty-eight percent of fatalities had evidence of other licit or illicit drug use (but not benzodiazepine use), and only 2% had evidence that they only used buprenorphine prior to death.

Summary of Toxic and Adverse Effects of Buprenorphine

The French experience with buprenorphine used for the treatment of opioid dependence suggests it is a safe and effective medication that has a mild side effect profile. Adverse effects can occur with its use, but these are generally at a low rate and those that occur most commonly are tolerable and consistent with buprenorphine's effects as a partial mu agonist.

Abuse of buprenorphine, especially by injection, increases the risk of adverse events and the potential for death. The most common clinical situation in France that has resulted in death has been the combination of buprenorphine with a benzodiazepine, both apparently taken by injection. This does not appear to be a pharmacokinetic interaction, but rather a pharmacodynamic effect with acute benzodiazepine use increasing the risk of respiratory depression produced by buprenorphine (Gueye *et al.*, 2002). It is also possible use of other psychotropic medications and/or the use of alcohol, in combination with buprenorphine and a benzodiazepine, further increases the risk of fatal respiratory depression.

While deaths associated with use of a prescription medication are extremely worrisome, it is important to note that the annual rate of 21 fatalities in patients with evidence of buprenorphine use occurs in the context of a decline of overdose deaths from 564 per year (in 1994) to 120 per day (in 2000) – that is, 444 fewer deaths per year, a remarkable achievement. Still, further efforts to improve the safety of buprenorphine are warranted, and potential means for achieving this goal in France include increased control of buprenorphine prescriptions, physician training on the risks of excessive dosing and co-prescription of other psychotropics with buprenorphine (especially benzodiazepines), and the development of new formulations such as tablets that contain naloxone and transdermal delivery systems.

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SYMPOSIUM XVI

DRUG CHOICE: WHAT WE KNOW AND WHAT WE NEED TO KNOW

S. S. Negus and W. L. Woolverton, Chairpersons

It has been said that all behavior, including drug use or abuse, is a choice among available options. Drug dependence is defined in large part by patterns of drug use that compromise expression of other, more adaptive behaviors. In this context, a goal of drug abuse treatment is not only to decrease drug use, but also to increase more adaptive behaviors. Reallocation of behavior can be achieved by manipulating the environment in which drug abuse occurs as well as by modifying the effects of the drug itself. Novel research strategies are being developed to explore the determinants of the choice to use drugs in complex environments, and novel treatment strategies are being developed to exploit these findings. This symposium addressed recent developments in the area of drug choice. William Woolverton (University of Mississippi Medical Center) described preclinical approaches to the study of drug choice in rhesus monkeys and compared the degree to which choice maintained by drug and non-drug reinforcers is governed by established behavioral processes. Steve Negus (McLean Hospital-Harvard Medical School) discussed environmental and pharmacological determinants of cocaine vs. food choice in rhesus monkeys and examined effects of candidate pharmacotherapies for cocaine dependence. Harriet de Wit (University of Chicago) described experimental approaches to the study of drug choice in human laboratory studies. Steve Higgins (University of Vermont) presented the results of clinical studies that sought to modify drug choice in humans by manipulating environmental variables. Gene Heyman (McLean Hospital, Harvard Medical School) served as discussant. An intriguing prospect of this research is that basic principles of addiction are being identified that may transcend the boundaries of any single drug and that may be generally applicable to the treatment of a wide range of addictive disorders.

SOME BEHAVIORAL ASPECTS OF DRUG CHOICE BY RHESUS MONKEYS

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Choice can be conceptualized as the situation in which two or more operant behaviors are maintained by different reinforcing stimuli available under various conditions. The laboratory analysis of choice maintained by non-drug reinforcers began in the late 1950s-early 1960s. Since that time, the field has grown substantially and is well developed and complex. The study of choice is not only scientifically intriguing, but also challenges very basic philosophical beliefs about ourselves, including our assumptions about free will and rational choice.

One of the goals of our research has been to understand drug choice in the context of theoretical views of choice that have evolved from research with non-drug reinforcers. There are main two concerns. One is the ongoing conceptual question in the drug self-administration field of the extent to which behavior maintained by drugs is comparable to behavior maintained by non-drug reinforcers. The second, really a derivative of the first, is as a framework for understanding some of the behavioral mechanisms that may contribute to "loss of control" of drug taking. One obvious weakness in the notion of "loss of control" as an experimental question is that it lacks an operational definition. An underlying premise of our research has been that loss of control can be defined as a situation in which the drug vs. non-drug choice deviates substantially from theoretical predictions of choice towards the drug option.

Among the theoretical views of choice that have evolved from the experimental analysis of behavior are matching, delay discounting, and behavioral economics. These were selected because of their theoretical breadth (matching) and because of their experimental currency (delay discounting and behavioral economics). The experimental analysis of choice began with the work of Herrnstein (1961). Pigeons were placed in a chamber containing two response keys. Pecking the keys resulted in food delivery under independent concurrent VI (conc VI) schedules. Pigeons apportioned their pecks according to the relative frequency of reinforcement. From this simple and elegant experiment was born the matching law. It has been revised, modified, and otherwise refined to account for a broad array of experimental variables, but still serves as a major organizing principle of choice. Baum (1974) proposed a major refinement, the generalized matching law, which is, perhaps, the most broadly applied statement of the matching law.

Our initial studies tested the hypothesis that behavior maintained by drug injections would conform the predictions of the generalized matching law. In a series of studies (Anderson, 2000; Woolverton, 1996, Woolverton and Alling, 1999), we found this to be the case when responding was maintained under a variety of conc VI schedules and by drugs from different pharmacological classes. In a recent study (Anderson *et al.*, in press), we tested the hypothesis that choice would deviate from matching when the two options were maintained by qualitatively different reinforcers (cocaine and food). In fact, responding was again well predicted by matching, with slight bias toward the cocaine option at the higher dose. We are now studying the cocaine:food choice using higher doses of cocaine.

Like matching, investigation of the effects of delay of reinforcement on choice began with Herrnstein (see Chung and Herrnstein, 1967). As before, pigeons were placed in a chamber containing two response keys. Pecking the keys resulted in food delivery under independent conc VI 1 min schedules. For one key, the delay was fixed and for the second key, delay was varied. As delay on the variable key increased, the proportion of responses emitted on that key decreased. The more delayed a reinforcer is, the less strongly it maintains behavior. Chung and Herrnstein (1967) proposed that relative responding "inversely matched" relative delay.

Since that time, the precise relationship between delay and reinforcer value has been the subject of a large amount of research. Delay matching generally has not been supported by the data. In fact, the effects of delay on relative reinforcement value are most nearly described by a hyperbolic delay-discounting equation proposed by Mazur (1987). This model has important implications for choice, for example, when applied to the choice often faced by drug abusers, i.e., the choice between a large, delayed reinforcer and a smaller, more immediate reinforcer. When both are temporally distant, the larger, more delayed reinforcer (e.g., a non-drug reinforcer) is preferred. But with the passage of time, the smaller more immediate reinforcer (e.g., the drug) increases in relative value until preference reverses. This model has been used to operationally define the change from self-controlled to impulsive choice and has been applied to substance abusers.

We have begun a series of studies designed to establish parameters of effects of delay and investigate the delay-discounting model. When monkeys chose between different doses of cocaine injected after equal delays, the higher dose was preferred. When choice was between equal doses injected after different delays, the more immediate injection was preferred virtually exclusively. The subjects did not match delay. When the high:low dose delay proportion remained constant at 3:1, preference switched to the lower dose at longer absolute delays. That is, the higher dose became relatively weaker as a reinforcer at longer absolute delays. Experiments are currently underway to assess the delay-discounting model with drugs as the reinforcers.

We have also begun experiments to study the effects of delay on the choice between a drug and a non-drug reinforcer (food). In the one monkey that has been studied to date, when the choice was between a delayed cocaine injection and immediate food, a delay of between 10 and 20 seconds was sufficient to eliminate cocaine choice. However, when the delay to food delivery was increased to 30 seconds, delays of up to 4.5 minutes did not decrease cocaine choice.

Based on these experiments, the following conclusions would be supported. Organisms tend to allocate drug choices according to frequency of reinforcement whether the alternative is a drug or a non-drug reinforcer. Additional research is needed to establish the generality of this conclusion for the drug:non-drug choice. Delay of reinforcement weakens a drug reinforcer, and delay and dose interact as determinants of drug choice. One exciting suggestion of our research is that a non-drug reinforcer more effectively competes with a drug reinforcer when it is delivered without delay.

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ENVIRONMENTAL AND PHARMACOLOGICAL MANIPULATION OF CHOICE BETWEEN COCAINE AND FOOD IN RHESUS MONKEYS

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Choice procedures have proven to be useful in the evaluation of the reinforcing effects of drugs, but data acquisition in preclinical choice procedures conducted in research animals has been relatively slow (Griffiths *et al.*, 1976; Johanson, 1976; Woolverton and Balster, 1979; Hart *et al.*, 2000). In view of this limitation and of the potential utility of choice procedures for the study of drug-maintained responding, the present study had three goals (Negus, submitted). The primary goal was to identify experimental conditions that would permit the study of choice between food and each of several cocaine doses within a single experimental session in rhesus monkeys. Such a procedure would permit a more rapid assessment of choice behavior than has been possible with previous procedures, which examined choice between food and only one drug dose during each experimental session (Griffiths *et al.*, 1976; Aigner and Balster, 1978; Woolverton and Balster, 1979). A second goal of the present study was to evaluate changes in cocaine vs. food choice produced by manipulation of three sets of environmental variables: (1) the schedules of reinforcement for cocaine and food, (2) the magnitude of the food reinforcer available during experimental sessions, and (3) the availability of non-contingent food and cocaine. Manipulation of some of these variables influenced choice between cocaine and food in previous studies (Nader and Woolverton, 1991; Nader and Woolverton, 1992b; Nader and Woolverton, 1992a), and the present study was designed to extend these earlier findings. The third goal of this study was to examine cocaine vs. food choice during treatment with candidate pharmacotherapies for cocaine dependence. On the basis of clinical experience with the treatment of opiate dependence, two general categories of treatment medications have been proposed (Rothman and Glowa, 1995). "agonist" medications produce some effects in common with the abused drug and may produce tolerance to and prevent withdrawal from the abused drug (e.g. methadone for the treatment of opiate dependence). "Antagonist" medications, in contrast, pharmacologically block the effects of the abused drug (e.g. naltrexone for the treatment of opiate dependence). In the present study, the monoamine releaser *d*-amphetamine was tested as a representative "agonist" medication, because it produces many cocaine-like effects and has a longer duration of action than cocaine (Colpaert *et al.*, 1979; Hoffman, 2001), and because several recent clinical studies reported promising results with *d*-amphetamine in the treatment of stimulant abuse (White, 2000; Grabowski *et al.*, 2001; Shearer *et al.*, 2001). Flupenthixol was tested as a representative "antagonist" medication, because it is a non-selective antagonist at D1 and D2 dopamine receptors that has also been evaluated as treatment for cocaine dependence (Soyka and DeVry, 2000; Evans *et al.*, 2001).

Daily 2hr sessions were divided into five components, and during each component, monkeys chose between i.v. cocaine (0-0.1 mg/kg/injection) and food (0, 1 or 3 food pellets). Up to 10 reinforcers were available during each component, and different discriminative stimuli were associated with each magnitude of each reinforcer. Under these conditions, cocaine choice was directly related to cocaine dose. Cocaine choice dose-effect curves could be determined in a single experimental session, and these choice dose-effect curves were stable through time. Cocaine choice could be increased by (1) making large cocaine doses available, (2) making cocaine inexpensive relative to food (i.e. by decreasing the relative fixed ratio requirement for cocaine), (3) decreasing the size of the alternative food reinforcer, (4) providing the alternative food reinforcer in abundance (which may decrease the reinforcing efficacy of the food), or (5) treating the monkeys with the dopamine receptor antagonist flupenthixol. Alternatively, cocaine choice could be decreased by (1) decreasing the magnitude of cocaine doses available, (2) making cocaine expensive relative to food (i.e. increasing the relative fixed ratio requirement for cocaine), (3) increasing the magnitude of the food reinforcer, or (4) treating monkeys with the candidate "agonist" medication d-amphetamine.

It is interesting to speculate about the degree to which these laboratory findings might have meaningful parallels to manipulations that promote or discourage drug use and abuse in humans. For example, drug use and drug abuse often flourish when drugs are inexpensive and readily available in high dose forms, and when alternative reinforcers are either very scarce (poverty) or very abundant (wealth). Alternatively, many government policies seek to limit drug abuse by limiting drug availability (e.g. by controlling drug production or distribution) and increasing the cost of drugs (e.g. by taxing legal drugs). Similarly, drug abuse treatments often employ both agonist medications (e.g. methadone, nicotine) and contingency management techniques that decrease the price of alternative reinforcers (e.g. by providing vouchers to reward drug abstinence). In particular, these findings are consistent with clinical studies suggesting the d-amphetamine may be useful as an agonist medication for the treatment of cocaine dependence. Overall, these results suggest that this cocaine vs. food choice procedure may be a useful tool for evaluating both environmental determinants of cocaine use and candidate pharmacotherapies for the treatment of cocaine abuse.

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DRUG CHOICE IN HUMANS

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Choice procedures are commonly used to assess drug preferences in humans, or to investigate preferences between drugs and other commodities such as money. The two most common goals of drug preference studies are i. to assess the reward value of a particular drug, and ii. to investigate non-pharmacological factors that affect drug-seeking behavior. Drug preference studies with humans share many features with preference studies using laboratory animals, both in methodology and in results. However, there are also several important differences, including the contribution of marked and sometimes uniquely human individual differences, and the influence of extra-experimental factors including prior expectancies, cognitions and beliefs about drugs. Unlike choice studies with non-humans, studies with humans provide the added opportunity to investigate an important feature of human drug use, i.e., the subjective experience that accompanies drug effects and the relationship between these subjective effects and drug-seeking behavior.

Preference for a drug in humans is determined by several factors, including the magnitude of reward of the drug and the alternative choice, the negative effects of the drug choice and the alternative choice, and the delay to the consequences of each and their probability of occurrence. Drug preference also depends on the current motivational state of the individual as well as on other, more lasting, trait-like individual characteristics. Examples of each of these factors are reviewed. Early studies (Johanson and Uhlenhuth, 1980) demonstrated that drugs with high potential for abuse, such as cocaine or amphetamine, are preferred over an inactive placebo capsule under double blind conditions. In contrast, drugs with a relatively low potential to be abused, such as benzodiazepines among normal healthy volunteers, are not chosen over a placebo capsule. In these studies in which the placebo capsule has little or no effect, the choices are determined primarily by the pleasant ("euphoria") or unpleasant ("dysphoria") effects of the active capsule. This idea is confirmed by the self-report measures of subjective effects collected in the same studies. In another variant of the drug-vs-placebo choice procedure, subjects are given the choice between drug and another commodity of known value, such as money (Higgins et al, 1996). In these studies, it can be shown that preference for a drug depends on the value of the alternative choice. As the value of the alternative choice increases, choice of even a highly-preferred drug, such as cocaine, decreases. These studies illustrate that drug preferences are not fixed but are *relative* to the value of the alternative choices. Drug preferences are also determined in part by the context in which the drug is taken and the degree to which a drug interferes with planned activities. Griffiths and colleagues (Jones et al, 2001) have shown that even highly preferred drugs such as cocaine will not be chosen if their effects interfere with planned activities. When subjects were required to relax after ingesting a capsule, they preferred a sedative-like drug, whereas when they were required to perform a vigilance task, they preferred a drug that facilitates good performance. These contextual determinants can influence preferences even for a highly preferred drug such as cocaine. Another factor that affects drug preference is the delay and probability of the reward deliveries. It is known that both delay and uncertainty decrease the value of rewards, and this has been demonstrated in human choice procedures. For example, Giordano *et al.*, (2001) recently showed that opioid addicts valued an immediate dose of an opiate agonist more than a delayed dose. Outcomes in choice procedures are similarly less valued if they are uncertain. Drug choice is also determined in part by characteristics of the individual, including both momentary fluctuations in state, and more stable, trait-like factors. For example, Higgins *et al.*, (1996) showed that pretreatment with one drug (e.g., alcohol) can influence choice of another drug (e.g., cocaine). In opiate addicts, the state of deprivation from opioids has been shown to increase preference for an opiate drug over money (Giordano *et al.*, 2001). Another key determinant of drug choice is the biological and experiential makeup of the individual organism. It is known that there are marked individual differences in responses to psychoactive drugs, including in the quality and magnitude of subjective or mood-altering effects of the drugs, and in the reinforcing effects of drugs. For example, the subjective effects of an acute dose of alcohol vary widely across individuals: Some individuals experience stimulant-like effects, whereas others experience only sedative effects. Notably, the subjects who experience stimulant-like effects exhibit a strong behavioral preference for the drug and report liking the effects, whereas those who experience sedation usually avoid choosing the drug in a preference test, and they report disliking the effects (Holdstock and de Wit, 1998; 1999; 2000). Why people differ in these responses to alcohol, or other drugs, is not known. The differences may stem from differences in personality, differences in neurobiological makeup, or from key experiences in the subjects' history. Controlled studies using drug choice procedures provide a powerful technique to study these various determinants of drug preferences.

Taken together, these studies illustrate the power and versatility of drug preference procedures in humans. Choice procedures can be used to assess the abuse liability of drugs, or to determine rewarding effects of drugs in potentially vulnerable populations. They can also be used to investigate the relationship between subjective effects of drugs and drug-seeking behavior, or the neurobiological basis of drug-seeking. Future studies may extend our understanding of the role of delay and probability in drug choice, and the role of delay and probability in vulnerable individuals or in high risk situations (e.g., stress). Together, these laboratory studies have the potential to advance our understanding of the factors that lead to pathological drug use, and to develop successful interventions to prevent or reduce drug use.

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CONCEPTUALIZING CONTINGENCY MANAGEMENT INTERVENTIONS IN TERMS OF CONCURRENT SCHEDULES

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Contingency management (CM) interventions in outpatient substance abuse treatment typically involve the delivery of non-drug reinforcers contingent on biochemically-verified abstinence from recent drug use. As such, these interventions can be conceptualized in terms of concurrent schedules of reinforcement. That is, patients residing in their natural environments make choices between continuing to self-administer the target drug or abstaining from drug use and collecting the alternative non-drug reinforcer offered by the clinic. An important benefit of conceptualizing CM in terms of concurrent schedules is that it integrates the approach with a larger body of basic behavioral science research that is well represented in this symposium.

My colleagues and I have conducted a number of randomized clinical trials on the efficacy of CM treatments for cocaine abuse. In conducting this research we were confronted by numerous empirical questions that either did not warrant or were not yet ready to be examined in a randomized clinical trial. Rather than just ignore these questions, we established a quasi-laboratory CM arrangement to investigate them. The arrangement is based on one originally developed by Stitzer and Bigelow (1982) in which cigarette smokers who are not currently trying to quit are asked to abstain from smoking for 5 consecutive days. Breath carbon monoxide (CO) levels are assessed 3 x/daily to verify recent smoking status. Because the vast majority of regular smokers cannot successfully abstain for even 24 hrs, this baseline provides an efficient and cost-effective method to examine the influence of CM or other interventions designed to increase smoking abstinence.

Among the issues we have investigated with this arrangement is the influence of the schedule of reinforcement delivery in CM interventions. In our original CM research with cocaine-dependent outpatients we developed a schedule in which the value of the incentive started at a relatively low value, increased with each consecutive test verifying recent abstinence, and reset to the original low level whenever testing indicated recent drug use (Higgins *et al.*, 1991). An important question was whether this relatively complex schedule was any more effective than a schedule in which a fixed-value incentive was delivered for each negative test result and withheld for positive test results. Two experiments were conducted to address this question (Roll *et al.*, 1996, 2000) Cigarette smokers were encouraged to abstain for 5 consecutive days and earned incentives according to the following schedules: escalating value with a reset contingency, escalating value without a reset contingency, a fixed value per negative test, or non-contingent delivery (independent of smoking status). Total potential earnings were kept constant across conditions. Abstinence was greater in all of the contingent conditions compared to the non-contingent control condition, but where the schedule of contingent reinforcement delivery made a difference was in whether subjects sustained an initial period of abstinence. More subjects sustained an initial period of abstinence through to the end of the study when incentives were delivered using the escalating value with the reset contingency compared to the other contingent payment schedules.

When CM was shown to be efficacious at increasing cocaine abstinence, questions were raised about the feasibility of extending CM to other difficult-to-treat populations. One such group was substance abusers with serious mental illness, a group for whom efficacious substance abuse treatments are sorely needed. Unfortunately, there is little experimental data available on drug use in this population. As a first step in evaluating the feasibility of using CM in this population, we invited schizophrenic cigarette smokers who were not currently trying to quit smoking to try to abstain from smoking for 5 consecutive days using the basic arrangement described above (Roll *et al.*, 1998). Smoking status was monitored several times daily via CO testing. Monetary incentives were earned contingent on recent smoking abstinence or non-contingently (i.e., independent of smoking status) across different experimental conditions. Abstinence was significantly greater when the incentives were delivered contingent on smoking abstinence, supporting the potential feasibility of CM interventions as an option for use with the seriously mentally ill. We recently replicated those results in cigarette smokers (Tidey *et al.*, in press) and extended them to schizophrenic marijuana smokers (Sigmon *et al.*, 2000).

Characterizing nicotine withdrawal is another area in which we have used this simple CM arrangement. Experimental studies on nicotine withdrawal are often compromised by subjects returning to smoking. To counter that problem, researchers sometimes place subjects in residential settings where smoking can be better regulated. However, smokers appear to experience less withdrawal when abstaining in hospital or other residential settings, perhaps due to the absence of familiar smoking-related stimuli. We recently demonstrated that smokers abstaining in their natural environments using the CM arrangements described above experience clinically-significant nicotine withdrawal, thereby underscoring the potential utility of CM as a research tool in this area of inquiry (Heil *et al.*, in press).

Finally, and perhaps bringing us full circle, the experience gained in promoting abstinence from cigarette smoking in these quasi-lab studies is proving fruitful in our newest area of treatment-outcome research where we are examining the efficacy of CM for promoting smoking cessation in pregnant cigarette smokers. Smoking during pregnancy is a leading cause of preventable fetal mortality and morbidity. Initial results from our group (Higgins *et al.*, in press) and others (Donatelle *et al.*, 2000) suggest that CM has important contributions to make in the treatment of this clinically challenging problem.

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A DISCUSSION OF DRUG CHOICE: WHAT WE KNOW AND WHAT WE NEED TO KNOW

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My comments will focus on three topics: the implications of the success of the voucher system in the treatment of substance dependence, how does the voucher system change drug users, and why choice procedures are essential for a general understanding of the reward value of a drug.

Higgins' voucher program demonstrates that incentives can persuade individuals who meet the criteria for substance dependence to markedly curb their drug use. Recreational opportunities and money turn out to be viable alternatives to drugs, even for those who are dependent. However, the definition of substance dependence suggests that this disorder's distinguishing feature is that drug use persists independently of its consequences. The definition reads (American Psychiatric Association, 1994): "The essential feature of Substance Dependence is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems." Following this passage is the statement that those who are dependent use drugs "compulsively." According to everyday speech (e.g., the dictionary), if drug use is compulsive, it is "irresistible." Yet, according to the voucher programs, drug use in addicts becomes resistible by linking abstinence with attractive non-drug alternatives. This would be unremarkable if it were assumed that addiction is a form of voluntary, albeit regretted consumption, but according to the APA, drug use in addicts is uncontrolled and compulsive. Something is amiss. Either the voucher programs are anomalous, creating patterns of behavior that have no generality, or the APA definition is overstated, failing to give due emphasis to the situational nature of drug use among those who meet the criteria for addiction.

We can decide the matter on the basis of data. There are many relevant clinical, historical, and experimental observations relevant to the question of whether those who are dependent use drugs compulsively or voluntarily. Let "voluntary" mean behavior that is susceptible to the influence of consequences, and consider the historical record. Following the Harrison Anti-Narcotics Act (1914) and the Surgeon General's Report (1964) on the health risks of smoking, there were large and dramatic decreases in drug consumption among addicted users. In the first instance, the consequences took the form of legal sanctions (Courtwright, 1982). In the second case, the consequences took the form of health risks and then the stigma that now accompanies smoking (e.g., Rozin, 1999). However, in both cases, drug use was curbed by new aversive consequences. Similar to these results, more than 80% of American soldiers who were regularly injecting heroin in Vietnam stopped doing so when they returned home. The enlisted men explained that they quit heroin because of the threat of arrest and other increased costs

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(Robins, 1993). Similar results have been obtained in the laboratory and clinic [see Heyman (1996, 2001) for reviews]. In each of these examples, aversive consequences curbed drug use in addicts. In the voucher programs, positive consequences for competing behaviors curbed drug use. In general, then, conditions can be arranged such that drug use in addicts is significantly influenced by its consequences.

The historical records suggest that the APA account of substance dependence misses the mark. The diagnostic criteria would be more accurate, if they read ". . .the individual *often* or *sometimes* continues use of the substance despite significant substance-related problems. . ." This statement implies that dependence is a situational state that, at its heart, entails an ambivalent relationship with drugs—with preference and consumption levels varying as a function of circumstances and other factors. The difference is that those who are ambivalent can be persuaded to do otherwise, those who are compulsive cannot.

The successes of the voucher programs raise interesting questions about the nature of psychological change. Many of those who preferred incentives to drugs continued to remain abstinent after the intervention was over. What has changed? Are they less impulsive? Or have they found substitute short-term rewards that provide as much kick as did the drugs? Put somewhat differently, did the voucher program engender a trait change (impulsivity) or a state change (patterns of behavior now incompatible with drug use). The answers to these questions would greatly increase our understanding of the voucher programs and, more generally, would add to our understanding of the plasticity of human nature.

The research of Woolverton, Negus, and de Wit provides information on the factors that influence preference for addictive drugs. The common feature in their studies is that the subjects have a choice between the drug and an effective non-drug reinforcer. But this is not how many drug-reward studies are carried out. In much of the research on the reward value of drugs, the subject is given a choice between drug and water (e.g., Pich *et al.*, 1997). As the subjects are not water deprived, the water has little if any reward value. Thus, there are studies in which drug choice is made in a relatively rich environment and in a relatively impoverished environment. In these next few paragraphs, I hope to prove to the reader that the studies conducted in the rich context are much more likely to provide useful information.

Research in operant psychology reveals a general relationship between rates of responding and rates of reinforcement, referred to as the matching law (Herrnstein, 1970). In its most general form, the matching law says that response rate is a hyperbolic function of reward rate: $B = kR/(R + R_e)$, where B is response rate, R is reward rate, and k and R_e are fitted constants. In the numerator, k is the response rate asymptote, and it varies as a function of the response requirement (e.g., lever weight) and state of the subject (e.g., drug dose). In the denominator R_e is the rate of reinforcement that maintains half-asymptotic responding, and it varies as a function of the reward (e.g., its magnitude), the reward value of competing activities, and the state of the subject (e.g., drug dose). For reviews of this literature, see Williams (1987) and Heyman (1990).

Now, consider what happens to response rate, when the environment, e.g., R_e, is sparse, providing little in the way of reward value. Response rate approaches its asymptotic value regardless of the size of the experimenter controlled reward, R. For example, if R_e is taken to its lower limit, 0.0, then response rate approaches its upper limit, k, regardless of the value of the reward provided by the experimenter. Experiments confirm this prediction (see, e.g., Herrnstein, 1970; Heyman & Monaghan, 1987). For example, in a study of alcohol reward, saccharin solutions maintained nearly asymptotic levels of responding when the competing reward was water, but virtually no responding when the competing reward was a weak sucrose solution (Heyman, 1997).

In other words, the hyperbolic functional relationship between rates of reward and rates of behavior implies that response rate is an insensitive measure of differences in reward value—unless precautions are taken. Fortunately, the equation, also gives us a simple recipe for the requisite precautions. The equation implies that experimenters should, as have Woolverton, Negus, and de Wit, add potent non-drug reinforcers. Note that as R_e gets bigger, response rate becomes an increasingly sensitive index of changes in the experimenter-arranged reward, R. For example, as R_e becomes increasingly large, changes in response rate begin to approximate a linear function of changes in reward rate. Moreover, one could develop cross-experiment, quantitative generality by using the same alternative reinforcer in different studies—for example, 10% sucrose as a gold standard. Thus, for experimenters interested in measuring the reward value of drugs, the correct choice is a choice procedure that employs an effective non-drug reinforcer. Or put another way, without a competing non-drug reinforcer it is not possible to tell if the drug of interest is an effective reward or merely better than nothing.

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BIOLOGICAL EVALUATION OF COMPOUNDS FOR THEIR PHYSICAL DEPENDENCE POTENTIAL AND ABUSE LIABILITY. XXVI. DRUG EVALUATION COMMITTEE OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE (2002)

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THE DRUG EVALUATION COMMITTEE (DEC)

Dr. A. Coop has held the position of Biological Coordinator of DEC since 1999. The duties of the Biological Coordinator involve receiving samples for evaluation, and distributing them blind to the relevant pharmacological groups within DEC. All data are received by the Biological Coordinator who maintains a confidential database, and forwards data to the submitters. Dr. Coop is the fourth DEC Biological Coordinator (the others were Drs. N. Eddy, E. May, and A. Jacobson). The other members of DEC are in the two analgesic testing groups, at Virginia Commonwealth University (VCU, Drs. L. Harris, M. Aceto, P. Beardsley) and the University of Michigan (UM, Drs. J. Woods [DEC Chair], J. Traynor), and three stimulant/depressant testing groups, at the University of Mississippi (UMS, Dr. W. Woolverton), University of Texas Health Science Center San Antonio (UTHSCSA, Drs. C. France, L. McMahon), and UM (Drs. G. Winger, J. Woods). Drs. T. Cicero and A. Jacobson act as emeritus members. DEC reports to the CPDD's Liaison Committee for Drug Testing and Evaluation (Dr. F. I. Carroll, Chair). Members of both the CPDD committee and other CPDD committees as well as NIDA staff, attend DEC's meeting held during the Annual Scientific Meeting of the CPDD. One other DEC meeting was held in Baltimore in May 2002 to discuss the work which has been accomplished, and future plans. Separate meetings are held at VCU quarterly with the members of the VCU Analgesic Testing Group, as well as Drs. E. May and E. Bowman, Dr. A. Coop, and a NIDA representative, to discuss the results obtained from the VCU testing and research program.

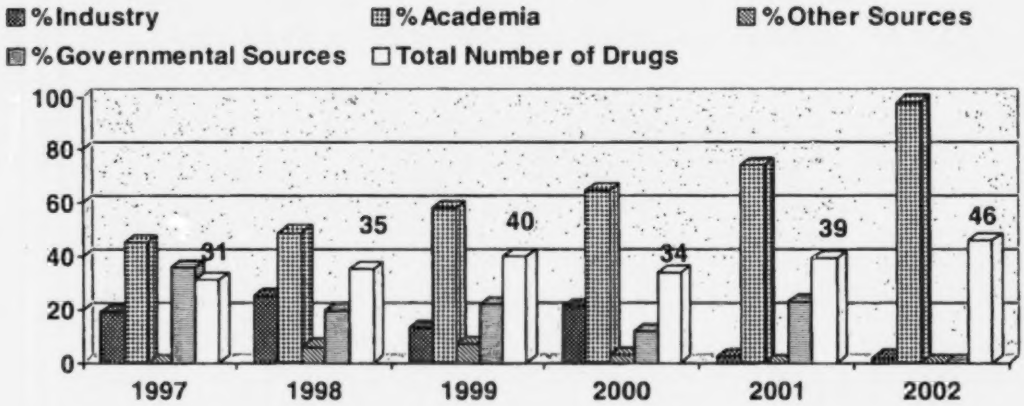
Data were released for publication this year on 46 different compounds evaluated by DEC's Analgesic Testing Program (Figure 1). Of these, 41 compounds were evaluated at VCU (antinociceptive assays in mice - tail flick, hot plate, and phenylquinone, and the tail-flick antagonist assay, as well as substitution for morphine and precipitated withdrawal assays in rhesus monkeys), and 37 at UM (binding affinity to the μ, δ, and κ opioid receptors, and GTPγS functional studies). Compounds came primarily from academia. The remaining compounds came from the pharmaceutical industry. Figure 1 clearly shows that the percentage of compounds originating from academia has been steadily increasing over the past few years, with the percentage from industry and governmental sources correspondingly decreasing. Four new submitters from academic institutions have provided compounds this year. Discussions between the Chair of DEC and governmental agencies have led to the anticipation that compounds from governmental sources will increase in future years as well. Two compounds which are metabolic precursors to gamma-hydroxybutyric acid (GHB) were released for publication this year by the groups in the Stimulant/Depressant Testing Program.

A joint publication based on the data gathered under DEC auspices from VCU, UM, and UMB, is currently in preparation (May *et al.*, 2002).

EXPERIMENTAL OBSERVATIONS

The names of the compounds that were released for publication this year are listed in Tables 1 and 2, and their molecular structures and a summary of their *in vivo* and *in vitro* data are in Tables 3 to 11. Similar to previous years (Coop 2002), the examined compounds are classified according to their molecular structure: indolomorphinans in Tables 3, 4, and 5; miscellaneous opioids in Table 6; 6,7-benzomorphans in Tables 7 and 8; esters of naltrexone in Table 9; analogs of gamma-hydroxybutyrate in Table 10. Compounds evaluated by the Stimulant/Depressant Testing Program are shown in Table 11. The more interesting compounds evaluated during the year are discussed below. For compounds that have been previously evaluated, the new data are discussed in relation to the published data.

FIGURE 1. DEC ANALGESIC TESTING PROGRAM: PERCENT AND SOURCE OF EXAMINED DRUGS AND TOTAL NUMBER OF COMPOUNDS (1997-2002)



The delta opioid selectivity (K_i ratio: mu/delta = 45) of the standard delta antagonist naltrindole (**NIH 10589**) in Table 3, is thought to be due to the indolic group (Portoghese *et al.*, 1990), and indeed the pyrazolo derivative **NIH 11050** (Table 3) shows no delta-selectivity. Interestingly, **NIH 11063** (Table 3), a naltrindole derivative containing a 14-methoxyl group and an *N*-propyl group, shows enhanced selectivity (K_i ratio: mu/delta = 250). This compound may find great use as a delta selective ligand in pharmacological assays. The related NIH **11064** (Table 3), with an *N*-cyclobutylmethyl group together with a 14-ethoxy and 5-methyl group, possesses equal selectivity as naltrindole, but has ten-fold reduced affinity at delta receptors.

NIH 11069 and **NIH 11070** (Table 4) are also analogs of naltrindole, but containing additional chlorinated aromatic rings. Both compounds proved to possess limited aqueous solubility, and a reliable *in vivo* assessment was not achieved. *In vitro* assays indicated that delta affinity and selectivity have been lost. Thus, the poor aqueous solubility, coupled with the low affinity, implies that such compounds will not find wide pharmacological use.

Table 5 shows *N'*-benzyl analogs of naltrindole. **NIH 11103** has previously been reported to be a long-acting delta antagonist (Korlipara *et al.*, 1994), but with the exception of **NIH 11104**, Table 5 shows that all derivatives display no delta antagonist activity after only 30 minutes, and no compound showed activity at 24 hours. These data show that there is no extended delta antagonism for these compounds, and indeed show little, if any, delta antagonism at all. It should be noted, however, that **NIH 11103** and **NIH 11104** showed toxic actions when administered i.c.v.

NIH 10967 (Table 6) is an amino-substituted tetrahydroisoquinoline, which shows potent antinociceptive effects in mice. The lack of opioid receptor binding, coupled with the fact that naloxone did not reverse the antinociception, indicates that these effects are not opioid.

The phenylpiperidine, **NIH 10996** (Table 6) demonstrates high affinity for mu opioid receptors and potent mu antagonism *in vitro*, yet is completely inactive as an opioid agonist or antagonist *in vivo*. This can be attributed to the presence of the acidic function on the *N*-substituent giving a zwitterionic species, thereby limiting transport into the CNS. NIH 10996 is thus an important lead for the development of peripherally restricted morphine antagonists (Schmidt, 2001). Peripherally restricted antagonists are of great interest as they are able to attenuate the severe constipatory effects of morphine in patients treated chronically with morphine, yet will not antagonize the desired analgesic effect.

Oxycodone (**NIH 11107** in Table 6) has been receiving a great deal of interest in both the scientific and non-scientific media, as Oxycontin®, a delayed release formulation containing a large dose of oxycodone, has become a drug of choice for opiate abusers because a large dose of oxycodone can be extracted and diverted for illicit purposes (Passik, 2001). NIH 11107 was previously studied by a previous incarnation of this committee in 1958 as

NIH 5710, and found to be morphine-like. The current study corroborates these data, showing that NIH 11107 completely substitutes for morphine, and is a selective mu agonist. Therefore, it is not surprising that oxycodone has found favor among opiate abusers.

A series of halogen-substituted *N*-benzyl benzomorphans is shown in Tables 7a and 7b. It has been previously reported that *N*-benzyl substituted benzomorphans display poor *in vivo* and *in vitro* opioid activity (May *et al.*, 1998), and the (+)-isomers tend to follow the same trend. It should be noted, however, that **NIH 11088** (Table 7b) has an unusually high affinity at kappa receptors (23 nM) for a (+)-opioid. The (-)-isomers in Table 7a are further examples of opioids possessing high affinity at mu and kappa receptors, yet no activity *in vivo*. **NIH 11097**, for example, possesses an affinity of 2.1 nM at kappa and 23.3 nM at mu receptors, yet fails to exert antinociceptive effects or morphine antagonism *in vivo*. The lack of kappa activity could be explained by the compound possessing low kappa efficacy, but the lack of *in vivo* mu activity is puzzling. As with NIH 10996, the *N*-benzyl substituted benzomorphans may be peripherally restricted, but there is no group in NIH 11097 which would be anticipated to prevent transport into the CNS. Further studies are required to investigate this intriguing profile.

(+)-Phenazocine (**NIH 11040**, Table 7b) is one of the few opioid (+)-isomers that is known to possess significant antinociceptive activity *in vivo*. A re-evaluation of NIH 11040 confirms a profile of antinociceptive activity in the mouse, but it does not substitute for morphine in dependent monkeys. The side-effects of slowing and jaw sag may suggest kappa agonist activity, which is consistent with NIH 11040 displaying higher affinity to kappa, than mu and delta receptors.

A series of *N*-allyl substituted benzomorphans are shown in Tables 8a and 8b. As expected the (+)-isomers in Table 8b display low affinity for opioid receptors, and little opioid activity in *in vivo* assays. The attenuation of withdrawal seen with **NIH 11043** and **NIH 11051** is probably a consequence of the non-opioid effects of these compounds masking withdrawal signs. **NIH 11032** and **NIH 11038** (Table 8a) both possess a methyl ether which can be metabolized to the more active phenol. NIH 11032 is active as a morphine antagonist in the mouse, but not in the monkey, whereas NIH 11038 is a weak morphine antagonist in the monkey, but is less active than NIH 11032 in the mouse. **NIH 11045** and **NIH 11096** (Table 8a) are esters corresponding to the methyl ether NIH 11038, and will be rapidly metabolized to the active phenol. As expected, morphine antagonism was observed in the mouse, but the assessment of NIH 11045 in the monkey was complicated by non-opioid CNS effects.

The esters of naltrexone (**NIH 11083** and **NIH 11084**, Table 9) would be expected to be rapidly metabolized to the active 3-phenols. NIH 11084 contains only a 3-ester, and the active metabolite would be naltrexone. NIH 11083 contains an additional ester group at the 14-position which would undergo metabolism far more slowly, making the active metabolite 14-acetoxynaltrexone which would be expected to possess greater lipophilicity than naltrexone. Thus, the greater morphine antagonist activity of NIH 11084 as compared to NIH 11083 can be rationalized in terms of it producing an active metabolite of greater lipophilicity and, therefore, greater CNS penetration.

The rise in recreational use and abuse of gamma-hydroxybutyrate (GHB) has led DEC to fully study the activity of this compound in previous years (1998, 2001). The scheduling of GHB has led to an increase in the use of metabolic precursors of GHB such as 1,4-butanediol (1,4-BDL) and gamma-butyrolactone (GBL) (Bernasconi *et al.*, 1999), and DEC has taken the lead in evaluating the activity of the precursors. 1,4-BDL has been evaluated by the analgesic group as **NIH 11030** (Table 10) and by the stimulant depressant group as **CPDD 0060** (Table 11). GBL has been reevaluated by the analgesic group as **NIH 11094** (Table 10) and by the stimulant depressant group as **CPDD 0061** (Table 11).

The activity of both compounds was very similar, with no activity in the analgesic assays, and little activity in the stimulant and depressant assays. It should be noted that in the pentobarbital discrimination assay severe sedation was observed at 300 mg/kg. These data reinforce the hypothesis that GHB acts through a yet to be determined mechanism of action, and underscores the need for the development of new and robust assays for evaluating the behavioral effects of GHB-like compounds.

TABLE 1. EVALUATED COMPOUNDS - ANALGESIC TESTING PROGRAM

NIH#	COMPOUND NAME	TABLE #-Evaluator
10589	Naltrindole.HCl	3-VCU
10967	8-(Ethylmethylamino)-5,6,7,8-tetrahydroisoquinoline.Oxalate	6-VCU/UM
10979	*N*-Cyclohexylethylnoroxymorphindole.HCl	3-UM
10996	(+)-2-[2(*S*)-Benzyl-3-[4(*R*)-(3-hydroxphenyl)-3(*R*),4-dimethylpiperidin-1-yl]propionamido]acetic acid	6-VCU/UM
11011	(+)-(1*S*,5*S*,9*S*)-2-(Cyclohexylmethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU
11012	(-)-(1*R*,5*R*,9*R*)-2-(Cyclohexylmethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU
11027	(-)-(1*R*,5*R*,9*R*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11029	(+)-(1*S*,5*S*,9*S*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11030	1,4-Butanediol (1,4-BDL)	10-VCU/SD
11032	(-)-(1*R*,5*R*,9*R*)-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan.oxalate	8-VCU/UM
11033	(+)-(1*S*,5*S*,9*S*)-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan.oxalate	8-VCU/UM
11036	(+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11038	(-)-(1*R*,5*R*,9*R*)-5,9-dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11039	(+)-(1*S*,5*S*,9*S*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11040	(+)-Phenazocine.HBr	7-VCU/UM
11041	(-)-(1*R*,5*R*,9*R*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11042	(+)-(1*S*,5*S*,9*S*)-2'-Acetoxy-2-(3-*cis*-chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan.oxalate	8-VCU/UM
11043	(+)-(1*S*,5*S*,9*S*)-2'-Acetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11044	(-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-2-(3-*cis*-chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan.oxalate	8-VCU/UM
11045	(-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.oxalate	8-VCU/UM
11050	17-Methyl-6,7-didehydro-3,14-dihydroxy-4,5α-epoxy-[(2-methyl)-pyrazolo-[6,7]]-morphinan.2HCl	3-UM
11051	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-propenyl)-2'-propionoxy-6,7-benzomorphan.HCl	8-VCU/UM
11052	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-propenyl)-2'-propionoxy-6,7-benzomorphan.HCl	8-UM
11063	4,5α-Epoxy-14β-methoxy-17-(propyl)indolo[2',3':6,7]morphinan-3-ol.HCl	3-VCU/UM
11064	17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-5β-methylindolo[2',3':6,7]morphinan-3-ol.HCl	3-UM
11069	1'-(2,6-Dichlorobenzyl)-14β-[(2,6-dichlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo[2',3':6,7]morphinan-3-ol.HCl	4-VCU/UM

11070	1'-(3-Chlorobenzyl)-14β-[(3-chlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo[2',3':6,7]morphinan-3-ol.HCl	4-VCU/UM
11080	(+)-(1*S*,5*S*,9*S*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11081	(-)-(1*R*,5*R*,9*R*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11082	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphanHCl	8-VCU/UM
11083	3,14-Diacetoxynaltrexone.oxalate	9-VCU/UM
11084	3-Propionylnaltrexone.oxalate	9-VCU/UM
11085	(+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl	8-VCU/UM
11088	(+)-(1*S*,5*S*,9*S*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11093	(-)-(1*R*,5*R*,9*R*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl	7-VCU/UM
11094	gamma-Butyrolactone (GBL)	10-VCU
11095	(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate	7-VCU/UM
11096	(-)-(1*R*,5*R*,9*R*)-2'-Butyroxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	8-VCU/UM
11097	(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate	7-VCU/UM
11098	(+)-(1*S*,5*S*,9*S*)-2'-Butyroxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl	8-VCU/UM
11103	1'-Benzylnaltrindole	5-VCU
11104	1'-Benzy-17-cyclopropylmethyl-14-hydroxy-4'-phenyl-[2',3':6,7]-pyrrolomorphinan	5-VCU
11105	1'-Benzyl-4,5,6,7-tetrahydronaltrindole	5-VCU
11106	1'-Benzyl-4,5,6,7-tetrahydrooxymorphindole	5-VCU
11107	Oxycodone.HCl	6-VCU/UM
11148	Oxymorphone.HCl	6-UM

TABLE 2. EVALUATED COMPOUNDS - STIMULANT/DEPRESSANT TESTING PROGRAM

CPDD#	COMPOUND NAME	TABLE #-Evaluator
0060	1,4-Butanediol (1,4-BDL)	11-S/D Group
0061	gamma-Butyrolactone (GBL)	11-S/D Group
0062	Melatonin	11-S/D Group

NOTES FOR TABLES 3 - 9

Salt forms are not shown. Rounded numbers are used; precise values and details of the procedures are given in the VCU, UM, and stimulant depressant reports (Aceto *et al.*, 2003; Woods and Traynor, 2003, McMahon and France, 2003). "Inactive" is stated when an ED_{50} or AD_{50} is not obtained. HP = hot plate assay; PPQ = phenylquinone antiwrithing assay; TF = tail flick assay; NTI = naltrindole (delta antagonist); norBNI = norbinaltorphimine (kappa antagonist); β–FNA = β-funaltrexamine (mu antagonist).

1) Antinociceptive reference data:
Morphine ED_{50} (mg/kg): Hot Plate = 0.8; Phenylquinone = 0.23; Tail-Flick = 5.8; Tail-Flick Antagonism vs. morphine (naltrexone AD_{50} = 0.007; naloxone AD_{50} = 0.035).

2) *In Vitro*:
Subtype selective binding affinity using recombinant receptors: μ (C_6 rat glioma cells expressing rat μ receptor), κ (CHO cells expressing human κ receptor), and δ (C_6 rat glioma cells expressing rat δ receptor). Affinity was assessed through the displacement of [^{3}H]-Diprenorphine. K_i values for standard ligands: μ (DAMGO 7.6 nM, morphine 11.2 nM); δ (SNC80 0.8 nM); κ (U69593 0.3 nM)

[^{35}S]GTPγS functional data were obtained employing recombinant receptors as described above. Values are given as EC_{50} with % stimulation compared to the standard full agonist (DAMGO, SNC80, U69,593), or the maximum stimulation achieved. μ (ED_{50}) morphine = 65 nM (100% stimulation), DAMGO = 34 nM (100% stimulation); δ (ED_{50}) SNC80 = 9 nM (100% stimulation), DPDPE = 8.3 nM (60% stimulation); κ (ED_{50}) U69,593 = 31 nM (100% stimulation), bremazocine = 0.5 nM (86% stimulation).

References to previous Drug Evaluation Committee annual reports are shown in parentheses, and refer to the actual year of publication.

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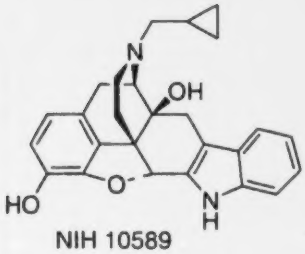
TABLE 3. INDOLOMORPHINANS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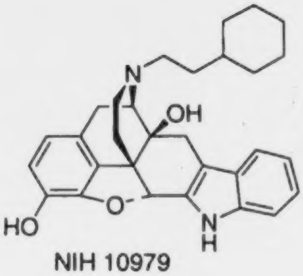
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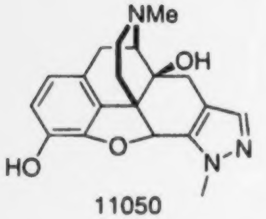
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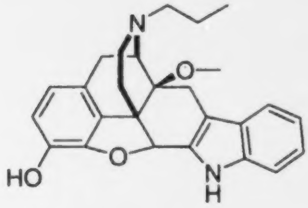
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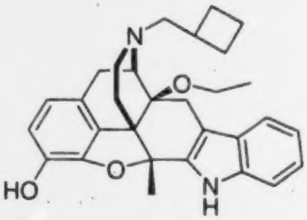
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ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg) | **IN VITRO** | **MONKEY**

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
10589[a,b]	-	Inactive[a]	Inactive[a]	Inactive[a]	μ=9.5, δ=0.21, κ=20.4[a]	Exacerbates withdrawal[a]
10979[d]	2.42[c]	0.39[c]	3.86[c]	-	μ=7.3, δ=181, κ=378[c]	-
11050	-	-	-	-	μ=23.9, δ=22.7, κ=157	-
11063	Inactive	Inactive	Inactive	Inactive	μ=270, δ=1.07, κ=108	-
11064	-	-	-	-	μ=182, δ=3.6, κ=128	-

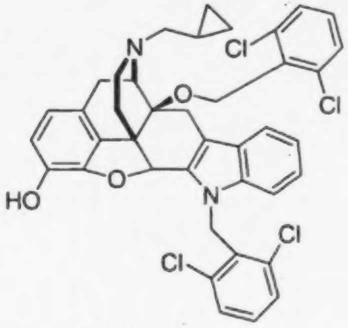
a) Previously reported as NIH 10589 (1990, 2000): pA_2 vs. DSLET = 9.44, pA_2 vs. sufentanyl = 7.71. Previously reported as NIH 10990 (2002) [^{35}S]GTPγS assay: AD_{50} vs. DAMGO = 7.9 nM.

b) New data: NIH 10589 vs. ED_{80} of SNC80 in PPQ: 30 min pretreatment AD_{50} = 1.69; 24 h. pretreatment inactive (s.c. and i.c.v.).

c) Previously reported (2002).

d) New data: [^{35}S]GTPγS assay: μ: EC_{50} = 105 nM (52% stimulation).

TABLE 4. INDOLOMORPHINANS



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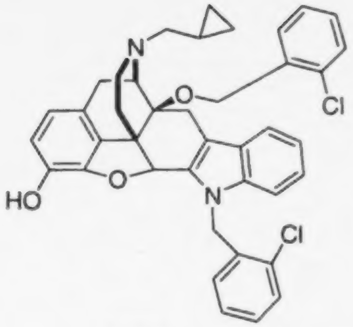
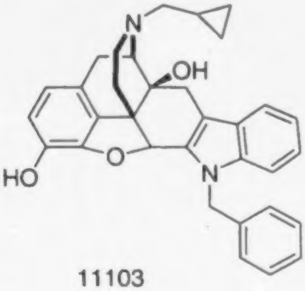


11070

	ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg)				IN VITRO	MONKEY
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11069[a]	-	-	-	-	μ=25.2, δ=62.7, κ=254	-
11070[b]	-	-	-	-	μ=192, δ=46.3, κ=627	-

a) Compound is not soluble enough for consistent results *in vivo*.
b) Compound is not soluble enough for consistent results *in vivo*.

TABLE 5. INDOLOMORPHINANS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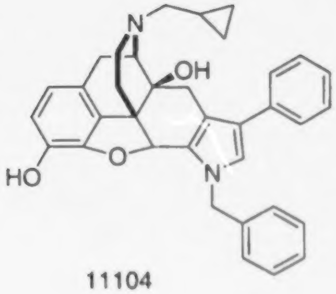
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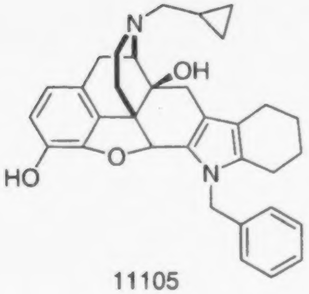
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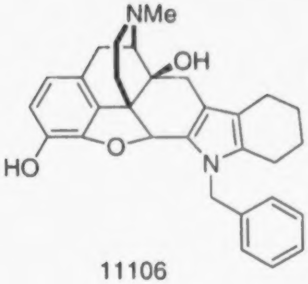
11106

DELTA OPIOID ANTAGONIST ASSAYS
(MOUSE AD_{50}: s.c., mg/kg or i.c.v. μg/brain)

NIH #	Antagonism of SNC80 ED_{80} in PPQ		
	30 min. pretreatment	24 h pretreatment	24 h pretreatment, i.c.v.
11103	Inactive[a]	Inactive	Inactive[b]
11104	4.34	Inactive	Inactive[c]
11105	Inactive	Inactive	Inactive
11106	Inactive	Inactive	Inactive

a) One mouse convulsed at 30 mg/kg (s.c.).
b) Lethal when given i.c.v. prior to SNC80.
c) One mouse died at 10 μg/brain.

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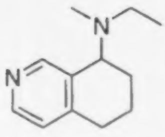
TABLE 6. MISCELLANEOUS OPIOIDS



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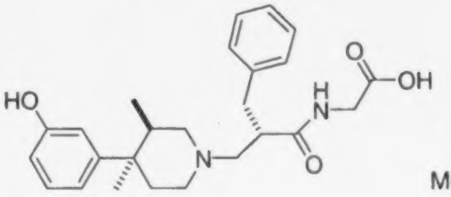

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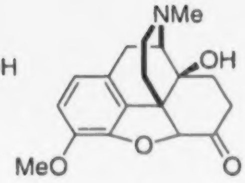

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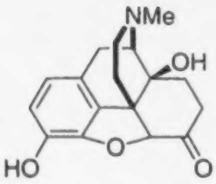


11148

ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg) **IN VITRO** **MONKEY**

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
10967[a]	0.8	0.37[b]	0.8	Inactive	$\mu,\delta,\kappa > 10,000$	-
10996	Inactive	Inactive[c]	Inactive[d]	Inactive	$\mu=0.41$, $\delta=235$, $\kappa=48.3$[e]	No substitution or exacerbation up to 20
11107[f]	1.37	0.38	0.94	Inactive	$\mu=485$, $\delta>3,000$, $\kappa>3,000$[g]	Complete substitution for morphine at 0.3[h,i]
11148[j]	-	-	-	-	$\mu=8.6$, $\delta=50.5$, $\kappa=93.5$[k]	See footnote[l]

a) Caused lethal convulsions in some mice.

b) Naloxone AD_{50} vs. ED_{80} of NIH 10967 in PPQ: Inactive.

c) 43% inhibition at 30 mg/kg; 69% at 60 mg/kg. Naloxone vs. ED_{69} of NIH 10996 in PPQ: inactive.

d) Inactive both s.c. and oral.

e) [^{35}S]GTPγS assay: no agonist activity at mu, kappa, and delta. Antagonism: mu: AD_{50} = 0.34 nM; kappa AD_{50} = 9.3 nM.

f) Previously published as NIH 5710 (1957) TF = 1.41 mg/kg; LD_{50} = 446.3 mg/kg. Complete substitution for morphine in monkeys. Potential for physical dependence: 1 mg/kg for 31 days followed by abrupt withdrawal gave rise to an abstinence syndrome similar to that of morphine.

g) [^{35}S]GTPγS assay: mu EC_{50} = 605 nM (88% stimulation).

h) Timecourse similar to morphine. Partial attenuation of withdrawal signs at 0.03 mg/kg.

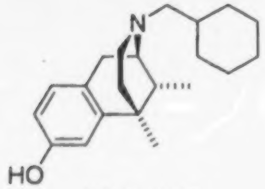
i) Respiratory depressant and a strong reinforcer in the monkey.

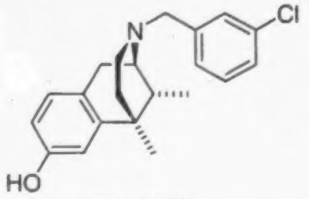
j) Previously evaluated as NIH 5501 (1956): TF = 0.17 mg/kg; LD_{50} = 182.7 mg/kg.

k) [^{35}S]GTPγS assay: mu EC_{50} = 32.2 nM (91% stimulation).

l) Respiratory depressant and a strong reinforcer in the monkey.

TABLE 7a. (-)-*N*-BENZYL-6,7-BENZOMORPHANS


NIH 11012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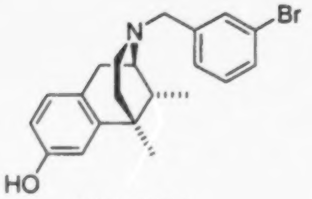
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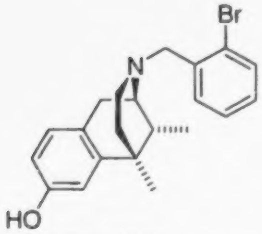
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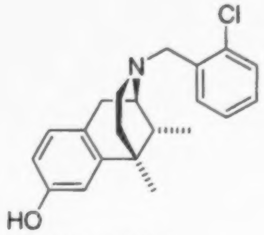
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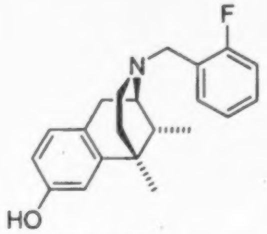

NIH 11097

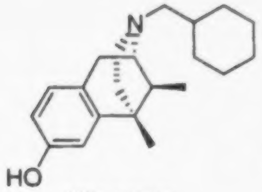
ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg) IN VITRO MONKEY

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11012[a,b]	Inactive[a]	14.62[a]	Inactive[a]	3.7[a]	μ=26, δ=315 κ=13[a]	Neither substituted nor exacerbated withdrawal at 0.75 and 3[a]
11027	Inactive	Inactive	Inactive	Inactive	μ=25.0, δ=1362, κ=11.1	Non-dose related exacerbation of withdrawal
11041	Inactive	Inactive	Inactive	Inactive	μ=47.7, δ=1326 κ=9.9	Neither substituted nor exacerbated withdrawal at 4 and 16
11081	Inactive	Inactive	Inactive	Inactive	μ=40.2, δ=1227 κ=13.5	-
11093	Inactive	Inactive	Inactive	Inactive	μ=16.8, δ=600, κ=17.5	-
11097	Inactive	Inactive	Inactive	Inactive	μ=23.3, δ=326, κ=2.1	-

a) Previously reported (2002). Jaw sag noted in the monkey at 3 mg/kg; tremors noted at 12 mg/kg.

b) New data: Antagonism of ED_{80} in PPQ by naltrindole - inactive.

TABLE 7b. (+)-*N*-BENZYL-6,7-BENZOMORPHANS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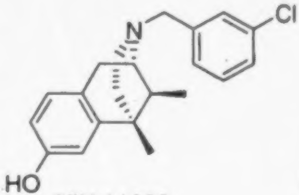
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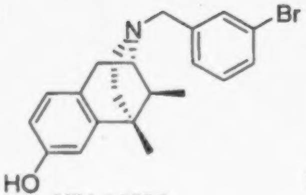
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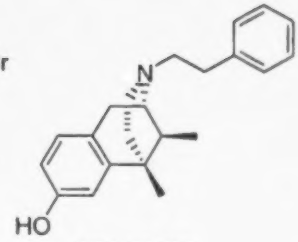
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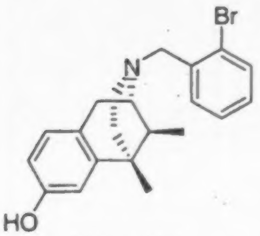
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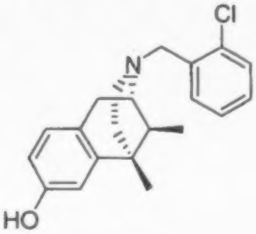
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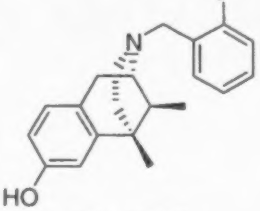
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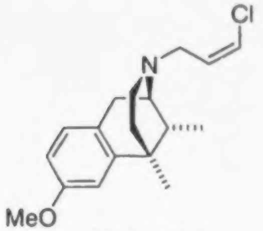
ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg) IN VITRO MONKEY

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11011[a,b]	Inactive[a]	17.57[a]	Inactive[a]	Inactive[a]	$\mu=568$, $\delta=5806$, $\kappa=83$[a]	Slight attenuation of withdrawal at 4 and 16. Salivation at 4; jaw sag at 16[a]
11029	Inactive	Inactive	Inactive	Inactive	$\mu=1223$, $\delta=6732$, $\kappa=347$	Partial attenuation of withdrawal at 4 and 16
11039	Inactive	Inactive	Inactive	Inactive	$\mu=745$, $\delta=3479$, $\kappa=255$	Neither substituted nor exacerbated withdrawal at 4 and 16
11040[c]	Inactive	3.4	8.75	Inactive	$\mu=126$, $\delta=875$, $\kappa=61$	Neither substituted nor exacerbated withdrawal at 1, 4, and 16.[d]
11080	Inactive	Inactive	Inactive	Inactive	$\mu=409$, $\delta=1853$, $\kappa=52.1$	Exacerbation of withdrawal at 16.
11088	Inactive	Inactive	Inactive	Inactive	$\mu=139$, $\delta=3565$, $\kappa=23.3$	-
11095	Inactive	Inactive	Inactive	Inactive	$\mu=560$, $\delta=4129$, $\kappa=47$	-

a) Previously reported (2002).
b) New data: Antagonism of ED_{80} in PPQ by naltrindole - inactive.
c) Previously reported as NIH 7614 (1961). TF = 6.63 mg/kg; LD_{50} = 200.7 mg/kg.
d) Jaw sag and slowing noted. One monkey convulsed at 1 and 4 mg/kg.

TABLE 8a. (-)-*N*-ALLYL-6,7-BENZOMORPHANS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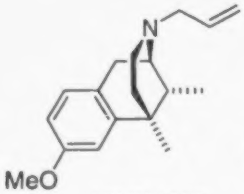
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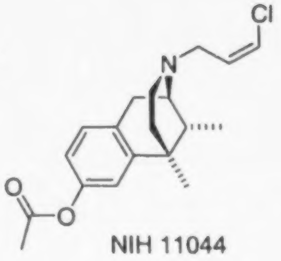
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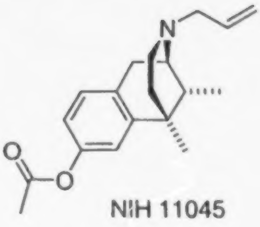
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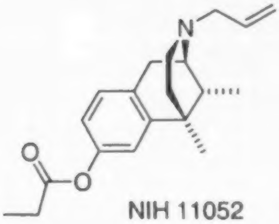
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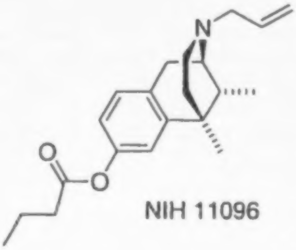
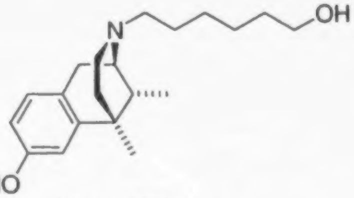

NIH 11096

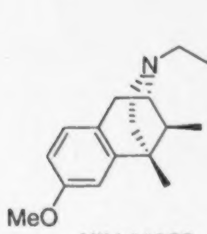

NIH 11082

ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg) IN VITRO MONKEY

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11032	Inactive	17.43	Inactive	1.08	μ=47.5, δ=105, κ=9.4	Neither substituted for morphine nor exacerbated withdrawal. Some jaw sag and slowing at 5
11038	Inactive	Inactive	Inactive	3.25[a]	μ=417, δ=763, κ=71.9	Exacerbation of withdrawal at 2[b,c]
11044	Inactive	10.50	Inactive	0.24	μ=14.9, δ=17.4, κ=3.0	Appeared to exacerbate withdrawal[c]
11045	Inactive	Inactive	Inactive	1.35	μ=136, δ=96.2, κ=29.2	Appeared to exacerbate withdrawal[c]
11052	-	-	-	-	μ=107, δ=90.7, κ=7.9	-
11082	Inactive	1.93	Inactive	Inactive	μ=10.2, δ=140, κ=28.6	-
11096	Inactive	Inactive	Inactive	0.29[d]	μ=30.2, δ=37.0, κ=0.9	-

a) Data with 30 minute pretreatment. With 4 h pretreatment, AD_{50} = 9.09 mg/kg.
b) Prompt onset of action, with a duration of 2.5h.
c) CNS effects made assessment difficult (slowing, eyelid ptosis, jaw sag).
d) Antagonist potency approx. 0.1x naloxone. Mild ataxia and hyperactivity seen at 30 mg/kg.

TABLE 8b. (+)-*N*-ALLYL-6,7-BENZOMORPHANS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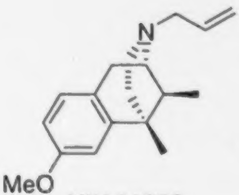
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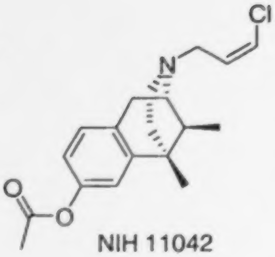
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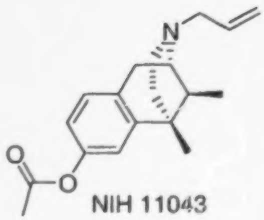
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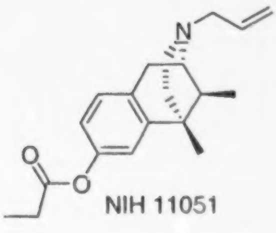
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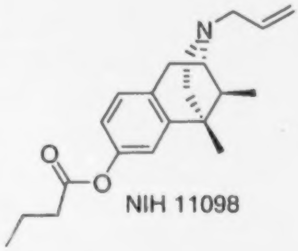
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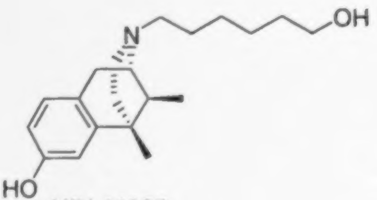
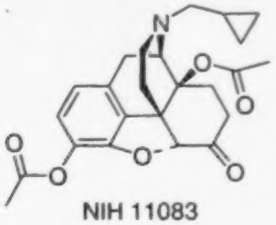

NIH 11085

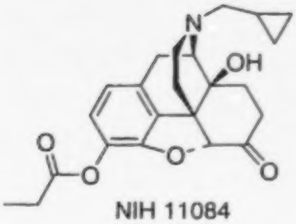
ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg)					IN VITRO	MONKEY
NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11033	Inactive	Inactive	Inactive	Inactive	μ=852, δ=1347, κ=296	No significant attenuation at 4 and 16[a]
11036	Inactive	21.6	Inactive	Inactive	μ=>10,000, δ=>10,000, κ=>10,000	Neither substituted nor exacerbated withdrawal at 4 and 16[a]
11042	Inactive	Inactive	Inactive	Inactive	μ=880, δ=1285, κ=196	Neither substituted nor exacerbated withdrawal at 4 and 16[a]
11043	Inactive	8.9	Inactive	Inactive	μ=2727, δ=>10,000, κ=>10,000	Attenuation of withdrawal at 16[a]
11051	Inactive	3.57	Inactive	Inactive	μ=3623, δ=>10,000, κ=4687	Attenuation of withdrawal at 16[a]
11085	Inactive	b	Inactive	Inactive	μ=598, δ=>10,000, κ=1476	-
11098	Inactive	9.6	Inactive	Inactive	μ=601, δ=3099, κ=1712	-

a) Jaw sag and ataxia noted at 16 mg/kg.
b) Erratic dose response

TABLE 9. ESTERS OF NALTREXONE



NIH 11083



NIH 11084

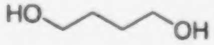
ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg) **IN VITRO** **MONKEY**

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11083	Inactive	Inactive	Inactive	0.0037[a]	μ=2.66, δ=134, κ=6.7	-
11084	Inactive	Inactive	Inactive	0.01[b]	μ=1.83, δ=82.3, κ=9.7	-

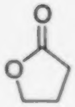
a) Short duration of action: % antagonism of morphine after administration of 0.03 mg NIH 11083: 30 min (88%), 2h (19%), 24h (0%). Potency approx. 10x naloxone.

b) Short duration of action: % antagonism of morphine after administration of 0.04 mg NIH 11084: 30 min (93%), 2h (24%), 24h (0%). Potency approx. equal to naloxone.

TABLE 10. ANALOGS OF GAMMA-HYDROXYBUTYRATE



NIH 11030



NIH 11094

ANTINOCICEPTIVE/ANTAGONIST ASSAYS (MOUSE ED_{50}/AD_{50}, s.c., mg/kg) **IN VITRO** **MONKEY**

NIH #	Hot Plate	Phenylquinone	Tail Flick	Tail Flick Antagonist	Binding Affinity, nM	Substitution-for-Morphine (s.c., mg/kg)
11030[a]	Inactive[b]	Inactive[b]	Inactive[b]	Inactive[b]	–	Neither substitutes for morphine nor exacerbates withdrawal at 4.5 and 18
11094[c]	Inactive	Inactive	Inactive	Inactive	–	-

a) Also evaluated by stimulant depressant group as CPDD0060.

b) NIH 11030 administered 20 and 60 minutes prior to testing.

c) Also evaluated by stimulant depressant group as CPDD0061. Previously reported as NIH 10540 (1988). TF: Inactive at 96 mg/kg; PPQ: $ED_{50} = 7.9$ mg/kg. Monkey: Neither substituted for morphine nor exacerbated withdrawal.

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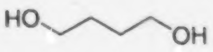
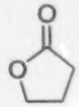
TABLE 11. EVALUATION OF STIMULANT/DEPRESSANT DRUGS



CPDD 0060



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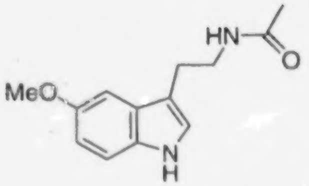

CPDD 0062

CPDD#	Discriminative Stimulus Effects in Monkeys. Comparison to Flumazenil & Midazolam (s.c.)	Monkey Self-Administration (iv)	Monkey Drug Discrimination (i.g.)
0060[a]	No benzodiazepine discriminative stimulus effects	No reinforcing effects in methohexital trained monkeys up to 3.2 mg/kg/inj	No substitution for pentobarbital up to 300 mg/kg. Monkeys sedated and ataxic at 300 mg/kg
0061[b]	No benzodiazepine discriminative stimulus effects	No reinforcing effects in methohexital trained monkeys up to 3.2 mg/kg/inj	No substitution for pentobarbital up to 300 mg/kg. Monkeys sedated and ataxic at 300 mg/kg
0062[c]	No benzodiazepine discriminative stimulus effects	No reinforcing effects in methohexital trained monkeys up to 3.2 mg/kg/inj	-

a) Also evaluated as NIH 11030 (See Table 10).

b) Also evaluated as NIH 11094 (See Table 10). Previously reported as NIH 10540 (1988).

c) Previously evaluated as NIH 10946 by the analgesic testing group (1999): Inactive in rodent and primate assays.

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EVALUATION OF NEW COMPOUNDS FOR OPIOID ACTIVITY (2002)

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This report contains information on opioid abuse liability evaluations of compounds that have been submitted to the Drug Evaluation Committee of the College and released for publication by the submitters. The information obtained usually involves *in vitro* evaluation in opioid binding assays. In addition, the compounds may be evaluated for discriminative and reinforcing effects. Analgesic and respiratory function assays are also possible. These behavioral assessments are conducted in rhesus monkeys. Usually when limited information is provided (*e.g.*, *in vitro* assessment only), it is because the sample provided by the submitter was insufficient to carry out further evaluation.

The evaluation of new compounds by the programs at the University of Michigan and the Medical College of Virginia or Virginia Commonwealth University is coordinated by Dr. A. Coop, University of Maryland. The compounds come originally from pharmaceutical companies, universities, government laboratories, and international organizations.

At the UM and MCV laboratories, drug samples arrive from the Biological Coordinator with only the following information: (1) an identifying NIH number, (2) molecular weight, (3) solubility information. After the evaluation is complete and the report submitted to Dr. Coop, the submitter is requested to release the chemical structure to include with the evaluation data in the ANNUAL REPORT. The submitter has up to three years before release of the structure is required. When the structure is released all of the data on the compound are reported herein.

OPIOID RECEPTOR BINDING AND IN VITRO EFFICACY ASSESSMENT

Details of the binding assay been described previously (Lee *et al.*, 1999). Briefly, aliquots of a membrane preparation are incubated with [^{3}H]diprenorphine (0.2 nM) in the presence of different concentrations of the drug under investigation at 25° C for 1 hr. Specific, *i.e.*, opioid-receptor-related binding is determined as the difference in binding obtained in the absence and presence of 10μM naloxone. The potency of the drugs in displacing the specific binding of the ^{3}H-ligand is determined from data using Graphpad Prism (GraphPAD, San Diego, CA) and converted to Ki values by the method of Cheng and Prussoff (1973). Opioid binding is performed in membranes from C_6 rat glioma cells expressing recombinant μ (rat; Emmerson *et al.*, 1994) or δ (rat; Clark *et al.*, 1997) and CHO cells expressing the recombinant κ (human, Zhu et al., 1997). The affinity (Kd) values of [^{3}H]diprenorphine at the receptors are: μ (0.15 nM); δ (0.45 nM); κ (0.25 nM).

The use of recombinant receptors means no cross-reaction with other receptors and allows for direct comparison with cellular functional assays. In the **ANNUAL REPORT**, the results of the selective binding assays are given as means ± SEM from three separate experiments, each performed in duplicate. Ki values for standard compounds using recombinant receptors and [^{3}H]diprenorphine as radioligand are: μ (DAMGO, 7.6 nM; morphine, 11.2 nM), δ (SNC80, 0.8 nM) and κ (U69593, 0.3 nM). If less than 50% displacement of [^{3}H]diprenorphine is seen at 10 μM it is reported as > 10 μM and the percent displacement given in parentheses.

[^{35}S]GTPγS assays are carried out using membranes from C6 cells expressing either μ (Emmerson *et al.*, 1996) or δ (Clark *et al.*, 1997) receptors or CHO cells expressing κ receptors (Zhu *et al.*, 1997). Assays are performed as described by Traynor and Nahorski (1995). Values are given as EC$_{50}$ with % effect compared to standard agonist (fentanyl, SNC80, or U69593) or as maximal stimulation achieved at 10 μM.

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EC_{50} values (nM) for standard compounds are as follows:

Mu receptor: morphine (65), DAMGO (34), fentanyl (13)
Delta receptor: SNC80 (9), DPDPE (8.3)
Kappa receptor: U69593 (31.0), bremazocine (0.5)

DPDPE (60%) and bremazocine (86%) are partial agonists compared with the standards SNC80 and U69593. Morphine and DAMGO give equivalent responses.

Antagonist activity is given as AD_{50} values or as pK_B values. AD_{50} refers to the concentration of test compound that reduces $[^{35}S]GTP\gamma S$ binding stimulated by an ED_{80} concentration of appropriate agonist (DAMGO, μ; DPDPE, δ; U69593, κ) by 50%. pK_B is the concentration of antagonist required to shift the dose-effect curve for appropriate agonist by 2-fold. It is a measure of the affinity of the antagonist for a receptor.

DRUG DISCRIMINATION IN RHESUS MONKEYS

We currently use three groups of monkeys to test the discriminative stimulus effects of submitted drugs: one of these groups discriminates the administration of the κ agonist ethylketazocine (EKC); a second group discriminates the μ agonist alfentanil or fentanyl; a third group is treated daily with morphine and discriminates the opioid antagonist naltrexone.

The procedures used with the EKC-trained monkeys have been described by Bertalmio *et al.* (1982). The monkeys are removed from their home cages each day and seated in primate restraining chairs. These chairs are placed in chambers equipped with two response levers, several stimulus lights and a cup to receive Noyes, banana-flavored pellets. These monkeys are required to make 100 consecutive responses on the correct one of the two levers and receive ten 300-mg food pellets. The right lever is correct if they were given a subcutaneous injection of 0.0032 mg/kg EKC immediately prior to the start of the cycle. The left lever is designated correct if they were given a sham injection before the start of the cycle. Each cycle lasts 15-min and consists of an initial 10-min black out period followed by a period of as long as 5 min, during which a blue light is illuminated in the chamber and the monkey can respond for food. If the food pellets are delivered before the 5 min period is completed, the lights are extinguished for the remainder of this time. Typically, a daily session consists of several 15 min cycles. During a training session, if EKC is given, it is given on the penultimate cycle of that session. Responding on the drug-appropriate lever is reinforced during that cycle and on the subsequent, final cycle of the day. These last two cycles may be preceded by from zero to four sham cycles on a training day. A training session of six sham cycles is also scheduled from time to time.

With this type of multiple, discrete-cycle training, the animals can be tested with a cumulative dosing procedure. On a test session, the first cycle is preceded by an injection of saline, and prior to subsequent cycles, increasing, cumulative doses of the test drug are administered. One hundred consecutive responses on either lever are reinforced throughout the test session. The test drug is administered in increasing doses until the monkey either responds on the drug-appropriate lever, the response rate falls to less than half of the saline-control rate, or six cycles are given. In the latter situation, it is assumed that the selected dose range is too low, and the test is continued at higher doses on the next test session. Each test session is preceded and followed by a training session. The criterion for satisfactory performance must be met on each training session that is followed by a test session. This criterion is that at least 90% of the responses during each cycle of a training session must be on the injection-appropriate lever, either sham or EKC.

The procedure for the alfentanil-trained monkeys is similar, but not identical. These animals are also trained and tested in a discrete, multiple-cycle procedure. The main difference between the alfentanil procedure and the EKC procedure is that the alfentanil monkeys are required to make 20 rather than 100 responses, and they receive a single pellet for correct responses. They can receive as many as 10 pellets during the 5-min, food-availability period of each cycle, but each pellet is delivered after 20 responses. Because in this procedure, monkeys can switch from one lever to another following the delivery of food, an additional criterion is added for satisfactory performance. In addition to making 90% or more of their responses on the correct lever, the monkeys must make fewer than 20 responses on the incorrect lever prior to delivery of the first food pellet of each cycle. Tests of the discriminative stimulus effects of submitted drugs in the alfentanil-trained monkeys are also done using a cumulative dosing procedure with dosing criteria identical to those used in the EKC-trained monkeys.

The procedure for studying discriminative stimulus effects in morphine-treated monkeys has been described previously (France and Woods, 1989). Daily sessions are comprised of a 10-min time out during which lever presses have no programmed consequence and a 5-min response period during which green stimulus lights are illuminated and signal the activation of a schedule of stimulus-shock termination. Sessions consist of between two and six discrete, 15-min cycles with each cycle. Under these experimental conditions electric shock is scheduled to be delivered to the subject's feet every 15 seconds; monkeys can terminate the lights and postpone scheduled shocks for 30 seconds by pressing five times consecutively (*i.e.*, fixed-ratio 5) the lever appropriate for the solution administered during the first minute of the time out (left lever, saline; right lever, naltrexone). Monkeys receive an injection of saline (0.1 ml/kg) or drug (0.0178 mg/kg naltrexone) during the first minute of each time out. On drug training days a single injection of naltrexone is administered during one time out and for that cycle and all subsequent cycles on that day only responding on the right lever postpones shocks. A variable number of saline cycles (0-5) precede the naltrexone cycle and on some days saline is administered during the time out of all cycles. Under these conditions monkeys switch their response choice from the saline lever to the naltrexone lever with complete generalization occurring in all three subjects at a dose of 0.01 mg/kg. Responding on the naltrexone lever is accompanied by other behavioral effects indicative of opioid withdrawal (*e.g.*, irritability, miosis, salivation). Moreover, when saline is substituted for the daily injection of 3.2 mg/kg of morphine monkeys respond predominantly on the naltrexone lever and show directly observable signs of withdrawal; the discriminative stimulus and other effects produced by morphine abstinence are reversed by some opioid agonists (*e.g.*, alfentanil; France and Woods, 1989; France *et al.*, 1990).

For test sessions increasing doses of drug are administered during the first minute of consecutive time outs and five consecutive responses on either lever postpone shocks. In monkeys that receive 3.2 mg/kg of morphine 3 hours earlier, increasing doses of a test compound are administered up to doses that produce an average of at least 80% responding on the naltrexone lever or to doses that disrupt responding and result in the delivery of electric shock. Drugs that do not substitute for naltrexone (*i.e.*, precipitate withdrawal) are also studied for their ability to reverse responding on the naltrexone lever in morphine-abstinent (*i.e.*, withdrawn) subjects. Test compounds are studied using a cumulative-dosing procedure in morphine-abstinent monkeys up to doses that reverse completely responding on the naltrexone lever (<20%) or to doses that disrupt responding. Some compounds that substitute for naltrexone also are studied for their capacity to prevent the effects of cumulative doses of opioid agonists. Monkeys that receive saline three hours earlier, rather than the daily injection of morphine, receive saline (control) or a single injection of test compound during the first cycle and increasing doses of agonist (alfentanil or morphine) during subsequent cycles. Agonists are administered up to doses that produce a switch from the naltrexone lever to the saline lever or to doses that disrupt responding and result in the delivery of electric shock.

THERMAL ANALGESIA IN RHESUS MONKEYS

The tail withdrawal procedure used to study analgesic effects of test compounds in rhesus monkeys has been described previously (Dykstra and Woods, 1986). Monkeys are restrained loosely at the neck and arms while seated in Plexiglas primate chairs. For tests of tail withdrawal latency, the lower 10-12 cm of the shaved tail is immersed in a thermos containing water at 40E, 50E, or 55E C and the latency until the tail is withdrawn from the thermos is recorded for each monkey at each temperature. When the tail is not withdrawn within 20 seconds (cut-off latency) the experimenter removes the thermos and a latency of 20 seconds is recorded. Experimental sessions begin with several exposures to 40EC water. Four or five monkeys are tested consecutively and the time between tail immersions for individual monkeys is 5 minutes. Generally, 40E C water does not produce tail withdrawal in rhesus monkeys (Dykstra and Woods, 1986); however, if a monkey fails to keep its tail in 40E C water for 20 seconds on at least 3 of 4 immersions, that animal is not tested further for that particular session. In a subsequent pre-test component, tails are immersed in 40E, 50E, and 55E C water. The order in which the three temperatures are presented is varied among subjects. If the latencies for tail withdrawal in the pre-test component are at or near 20 seconds for 40E C water and less than 5 seconds for 55E C water, monkeys receive the test compound. The test is identical to the pre-test, except that monkeys receive s.c. injections of drug 10 minutes prior to tail immersion. The time between immersions for individual subjects is 5 minutes or less and the order in which temperatures are presented varies among subjects and across cycles. The interinjection interval typically is 30 minutes and between four and six doses are studied in a single experiment using the cumulative dosing procedure. For some studies a single dose of an opioid antagonist is administered prior to the test compound and for other studies a single dose of test compound is administered prior to increasing doses of a μ (*e.g.*, alfentanil) or κ (*e.g.*, U-50,488) opioid agonist.

RESPIRATORY STUDIES IN RHESUS MONKEYS

The effects of test compounds on ventilatory function are studied in rhesus monkeys breathing air or 5% CO_2 in air (France and Woods, 1990; Howell *et al.*, 1988). Monkeys are restrained at the neck and waist while seated in a Plexiglas primate chair. Normal air or 5% CO_2 in air is delivered at a rate of 10 l/min into a sealed helmet placed over the subject's head. Changes in pressure within the helmet are measured and recorded by a transducer and a microprocessor, and are transformed according to known standards to frequency of respiration (f) in breaths/minute and to tidal volume (V_T) in ml/inspiration. Data are recorded continuously during 23-minute exposures to air alternating with 7-minute exposures to CO_2. The last 3 minutes of exposure to CO_2 are used for data analyses and are compared to the last 3 minutes of exposure to air only. Increasing doses of drug are administered during the first minute of consecutive time outs so that the interinjection interval is 30 minutes. For some studies a single injection of an opioid antagonist is administered prior to increasing doses of a test compound and for other studies a single injection of test compound is administered prior to cumulative doses of a standard compound (*e.g.*, alfentanil).

SELF-ADMINISTRATION BY MONKEYS

Tests of self-administration determine the ability of the drug to maintain responding in monkeys trained to self-inject codeine. Each of at least three monkeys is studied with saline as a negative control and a number of doses of the test compound until a maximum rate of responding was obtained or until, in the absence of evidence of a reinforcing effect, observable changes in behavior are produced by the compound.

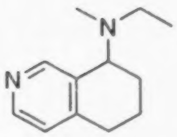
The schedule of intravenous drug delivery is a fixed-ratio 30; when a light above a lever is illuminated, the 30th response produce an intravenous drug injection accompanied by another light that is illuminated during drug delivery. After each injection, a 45 sec timeout period occurs. A component of the session ends after 20 injections have been received or 25 min have passed, whichever occurs first. Different doses of the drug are available during each of four components of a session. Other procedural details are given in Winger *et al.* (1989).

SUMMARY OF COMPOUNDS EVALUATED

The compounds that were evaluated at the University of Michigan during the past year are shown in the following Table. Also shown are dates of Reports to the Biological Coordinator in which results are reported.

NIH #	Date Submitted to Biological Coordinator	NIH #	Date Submitted to Biological Coordinator
10967	5 April 1999	11053	25 November 2001
10996	28 April 2000	11065	25 November 2001
11027	14 March 2001	11069	15 January 2001
11029	14 March 2001	11070	15 January 2002
11032	14 March 2001	11080	4 January 2002
11033	14 March 2001	11081	4 January 2002
11036	14 March 2001	11082	15 January 2002
11038	11 April 2001	11083	15 January 2002
11039	2 November 2001	11084	15 January 2002
11040	22 October 2001	11085	15 January 2002
11041	22 October 2001	11088	15 January 2002
11042	30 October 2001	11093	14 March 2002
11043	23 October 2001	11095	14 March 2002
11044	24 October 2001	11096	6 May 2002
11045	24 October 2001	11097	14 March 2002
11050	23 October 2001	11098	14 March 2002
11051	23 October 2001	11107	1 May 2002
11052	23 October 2001	11148	1 May 2002

NIH 10967 **8-(Ethylmethylamino)-5,6,7,8-tetrahydroisoquinoline.oxalate**



OPIOID RECEPTOR BINDING (nM)

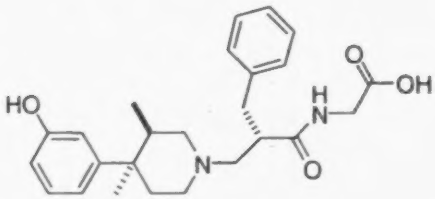
μ-receptor: >10 (39.0 ± 1.6% inhibition at 10 μM)
δ-receptor: >10 (-2.0 ± 2.2% inhibition at 10 μM)
κ-receptor: >10 (10.7 ± 5.6% inhibition at 10 μM)

SUMMARY

NIH 10967 had no affinity for opioid receptors.

* * *

NIH 10996 **(+)-2-[2(*S*)-Benzyl-3-[4(*R*)-(3-hydroxphenyl)-3(*R*),4-dimethylpiperidin-1-yl]propionamido] acetic acid**



OPIOID RECEPTOR BINDING (nM)

μ-receptor:	0.41 ± 0.16
δ-receptor:	235 ± 28.4
κ-receptor:	48.3 ± 3.0

[^{35}S]GTPγS ASSAY

Agonist Activity

μ-receptor: no agonist activity up to 10 μM
κ-receptor: no agonist activity up to 10 μM

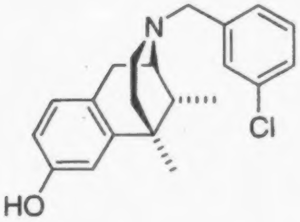
Antagonist Activity

μ-receptor: $AD_{50} = 0.34 \pm 0.04$ nM
κ-receptor: $AD_{50} = 9.3 \pm 1.8$ nM

SUMMARY

NIH 10996 is a highly potent μ antagonist, with 27-fold selectivity over κ receptors. Binding studies indicate a 118-fold selectivity for μ over κ receptors and a 570-fold selectivity over δ receptors.

NIH 11027 (-)-(1*R*,5*R*,9*R*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

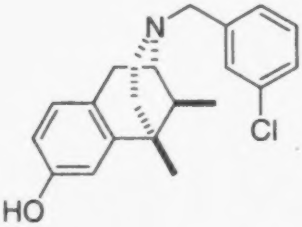
μ-receptor: 25.0 ± 9.9
δ-receptor: 1362 ± 53
κ-receptor: 11.1 ± 3.2

SUMMARY

NIH 11027 has high affinity for κ and μ receptors with high selectivity (δ/κ = 123; δ/μ = 55) for both of these over δ receptors.

* * *

NIH 11029 (+)-(1*S*,5*S*,9*S*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl



OPIOID RECEPTOR BINDING (nM)

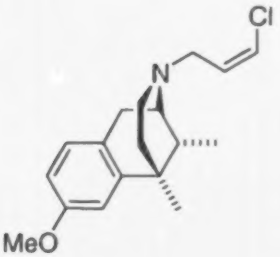
μ-receptor: 1223 ± 411
δ-receptor: 6732 ± 453
κ-receptor: 347 ± 39

SUMMARY

NIH 11029 has low affinity for κ > μ opioid receptors and very low affinity for δ receptors.

* * *

NIH 11032 (-)-(1*R*,5*R*,9*R*)-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan.oxalate



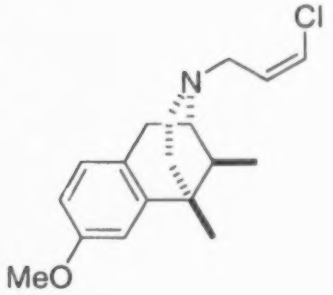
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 47.5 ± 11.0
δ-receptor: 105 ± 11.9
κ-receptor: 9.4 ± 1.0

SUMMARY

NIH 11032 has κ receptor affinity with limited selectivity over μ and δ receptors.

NIH 11033 (+)-(1*S*,5*S*,9*S*)-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan.oxalate



OPIOID RECEPTOR BINDING (nM)

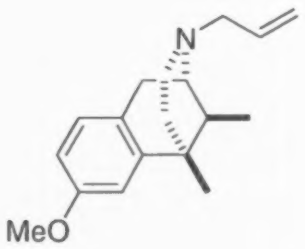
μ-receptor: 852 ± 294
δ-receptor: 1347 ± 370
κ-receptor: 296 ± 78.8

SUMMARY

NIH 11033 has low affinity for opioid receptors in the order κ > μ > δ.

* * *

NIH 11036 (+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan.oxalate



OPIOID RECEPTOR BINDING (nM)

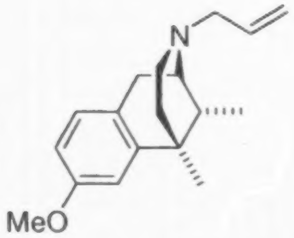
μ-receptor: >10 (37.5% inhibition at 10 μ M)
δ-receptor: >10 (25% inhibition at 10 μ M
κ-receptor: >10 (22% inhibition at 10 μ M)

SUMMARY

NIH 11036 has very low affinity for opioid receptors.

* * *

NIH 11038 (-)-(1*R*,5*R*,9*R*)-5,9-dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan.oxalate



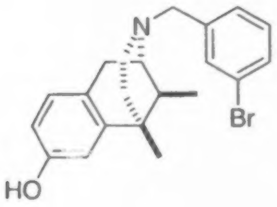
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 417 ± 74
δ-receptor: 763 ± 109
κ-receptor: 71.9 ± 29

SUMMARY

NIH 11038 has some affinity for κ receptors and is 6- 10-fold selective for κ over μ or δ receptors.

NIH 11039 **(+)-(1*S*,5*S*,9*S*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (μM)

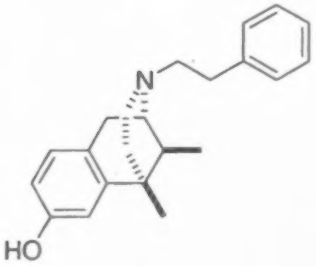
μ-receptor:	745 ± 231
δ-receptor:	3479 ± 106
κ-receptor:	255 ± 25

SUMMARY

NIH 11039 has weak affinity for κ receptors, lower affinity at μ receptors and is very weak at δ receptors.

* * *

NIH 11040 **(+)-Phenazocine.HBr**



OPIOID RECEPTOR BINDING (nM)

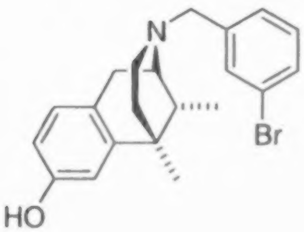
μ-receptor:	126 ± 49
δ-receptor:	875 ± 275
κ-receptor:	61.1 ± 8.8

SUMMARY

NIH 11040 has some affinity for κ > μ receptors and is weaker at δ receptors, with 14-fold κ/δ selectivity, but only 2-fold κ/μ selectivity

* * *

NIH 11041 **(-)-(1*R*,5*R*,9*R*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**



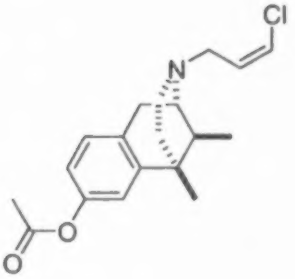
OPIOID RECEPTOR BINDING (nM)

μ-receptor:	47.7 ± 21.1
δ-receptor:	1326 ± 53.3
κ-receptor:	9.9 ± 1.4

SUMMARY

NIH 11041 has high affinity for κ receptors. It is 5 times weaker at μ receptors and 26 times weaker at δ receptors.

NIH 11042 **(+)-(1*S*,5*S*,9*S*)-2'-Acetoxy-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan. oxalate**



OPIOID RECEPTOR BINDING (nM)

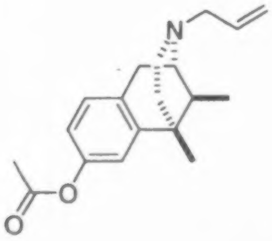
μ-receptor: 880 ± 263
δ-receptor: 1285 ± 173
κ-receptor: 196 ± 62

SUMMARY

NIH 11042 has some affinity for κ receptors with 4-6 times lower affinity for μ and δ receptors.

* * *

NIH 11043 **(+)-(1*S*,5*S*,9*S*)-2'-Acetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.oxalate**



OPIOID RECEPTOR BINDING (nM)

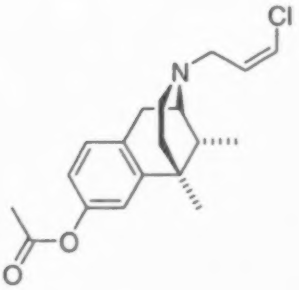
μ-receptor: 2723 ± 981
δ-receptor: >10 (38 ± 2.7% inhibition at 10 μM)
κ-receptor: >10 (53 ± 2.3% inhibition at 10 μM)

SUMMARY

NIH 11043 has low affinity for μ > κ and δ receptors.

* * *

NIH 11044 **(-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan.oxalate**



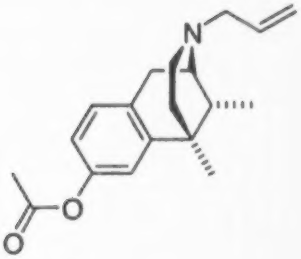
OPIOID RECEPTOR BINDING (nM)

μ-receptor: 14.9 ± 2.5
δ-receptor: 17.4 ± 2.3
κ-receptor: 3.0 ± 0.1

SUMMARY

NIH 11044 has high affinity for κ opioid receptors > μ = δ receptors, with a selectivity of 5-fold for κ receptors over the other types.

NIH 11045 **(-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.oxalate**



OPIOID RECEPTOR BINDING (nM)

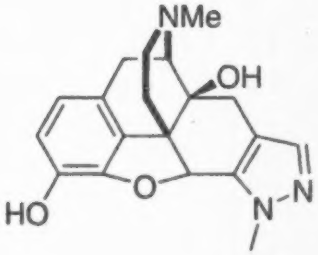
μ-receptor: 136 ± 34
δ-receptor: 96.2 ± 8.1
κ-receptor: 29.2 ± 1.6

SUMMARY

NIH 11045 has affinity for κ opioid receptors but is only 3-4-fold selective for the κ over δ and μ receptors.

* * *

NIH 11050 **17-Methyl-6,7-didehydro-3,14-dihydroxy-4,5α-epoxy-[(2-methyl)-pyrazolo-[6,7]]-morphinan.2HCl**



OPIOID RECEPTOR BINDING (nM)

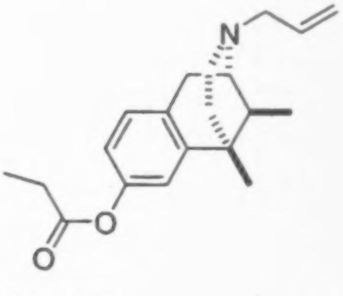
μ-receptor: 23.9 ± 10.1
δ-receptor: 22.7 ± 3.3
κ-receptor: 157 ± 53.0

SUMMARY

NIH 11050 has the same affinity for μ and δ receptors with no selectivity. It is approximately 7-times weaker at κ receptors.

* * *

NIH 11051 **(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-propenyl)-2'-propionoxy-6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (nM)

μ-receptor: 3623 ± 1175
δ-receptor: >10 (33.2 ± 0.4% inhibition at 10 μM)
κ-receptor: 4687 ± 329

SUMMARY

NIH 11051 has poor affinity for opioid receptors.

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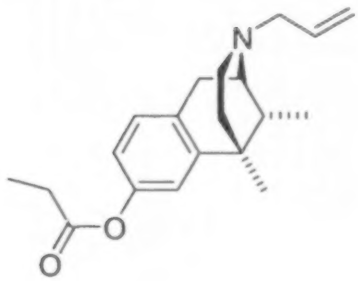
NIH 11052 **(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-propenyl)-2'-propionoxy-6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (nM)

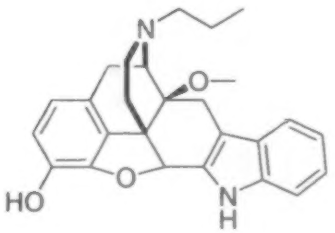
μ-receptor:	107 ± 42
δ-receptor:	90.7 ± 15.4
κ-receptor:	7.9 ± 0.7

SUMMARY

NIH 11052 has high affinity for κ opioid receptors and is 12-times selective for κ over μ or δ receptors.

* * *

NIH 11063 **4,5α-Epoxy-14β-methoxy-17-(propyl)indolo[2',3':6,7]morphinan-3-ol.HCl**



OPIOID RECEPTOR BINDING (nM)

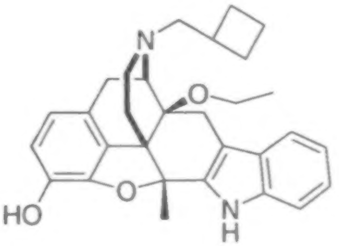
μ-receptor:	270 ± 20.3
δ-receptor:	1.07 ± 0.18
κ-receptor:	108 ± 5.3

SUMMARY

NIH 11063 has high δ-receptor affinity and selectivity. It is 100-fold selective for δ over κ and 250-fold selective for δ over μ.

* * *

NIH 11064 **17-Cyclobutylmethyl-4,5α-epoxy-14β-ethoxy-5β-methylindolo[2',3':6,7]morphinan-3-ol.HCl**



OPIOID RECEPTOR BINDING (nM)

μ-receptor:	182 ± 28.4
δ-receptor:	3.6 ± 0.9
κ-receptor:	128 ± 11.0

SUMMARY

NIH 11064 has high δ receptor affinity and good selectivity. It is 50-fold more selective for δ over κ and 36-fold selective for δ over μ.

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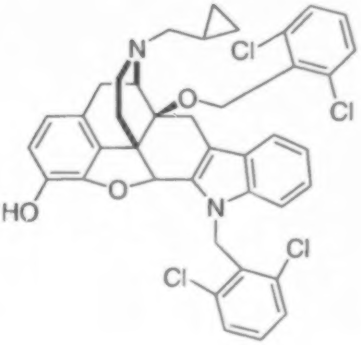
NIH 11069 **1'-(2,6-Dichlorobenzyl)-14αβ-[(2,6-dichlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo [2',3':6,7]morphinan-3-ol.HCl**



OPIOID RECEPTOR BINDING (nM)

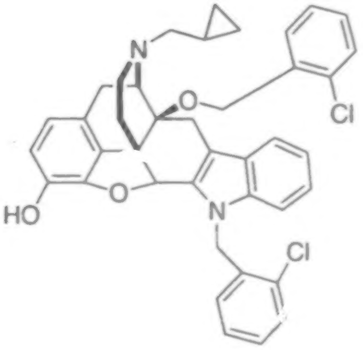
μ-receptor: 25.2 ± 5.1
δ-receptor: 62.7 ± 16.9
κ-receptor: 254 ± 69

SUMMARY

NIH 11069 has affinity for μ and δ receptors (with minimal selectivity) and lower affinity for the κ receptor.

* * *

NIH 11070 **1'-(3-Chlorobenzyl)-14β-[(3-chlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo [2',3':6,7]morphinan-3-ol.HCl**



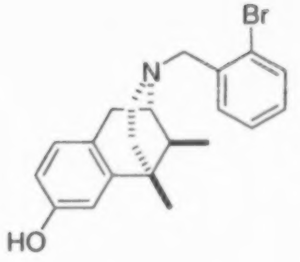
OPIOID RECEPTOR BINDING (μM)

μ-receptor: 192 ± 87
δ-receptor: 46.3 ± 6.5
κ-receptor: 627 ± 92

SUMMARY

NIH 11070 has affinity for the δ-receptor > μ > κ.

NIH 11080 **(+)-(1*S*,5*S*,9*S*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (μM)

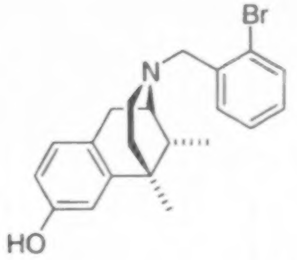
μ-receptor:	409 ± 76
δ-receptor:	1853 ± 101
κ-receptor:	52.1 ± 11.3

SUMMARY

NIH 11080 has affinity for the κ receptor. It has 8-fold less affinity for the μ receptor and 36-fold less affinity for the δ receptor.

* * *

NIH 11081 **(-)-(1*R*,5*R*,9*R*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (nM)

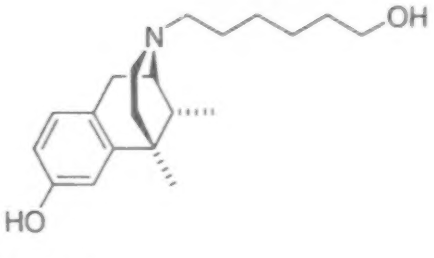
μ-receptor:	40.2 ± 4.4
δ-receptor:	1227 ± 138
κ-receptor:	13.5 ± 2.0

SUMMARY

NIH 11081 has high affinity for κ > μ receptors, but has weak affinity for the δ receptor.

* * *

NIH 11082 **(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl**



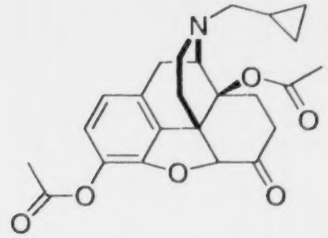
OPIOID RECEPTOR BINDING (nM)

μ-receptor:	10.2 ± 0.73
δ-receptor:	140 ± 15.8
κ-receptor:	28.6 ± 4.5

SUMMARY

NIH 11082 has high affinity for μ and κ with lower affinity for the δ receptor.

NIH 11083 3,14-Diacetoxynaltrexone.oxalate



OPIOID RECEPTOR BINDING (nM)

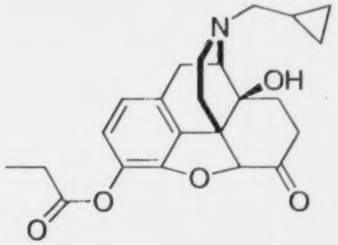
μ-receptor: 2.66 ± 0.12
δ-receptor: 134 ± 37.7
κ-receptor: 6.7 ± 2.0

SUMMARY

NIH 11083 has high affinity for μ and κ receptors with lower affinity for the δ receptor.

* * *

NIH 11084 3-Propionoxynaltrexone.oxalate



OPIOID RECEPTOR BINDING (nM)

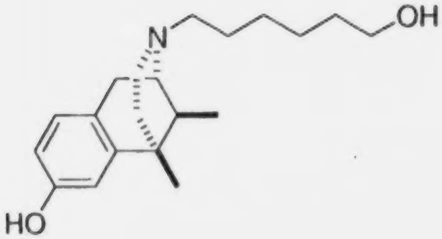
μ-receptor: 1.83 ± 0.18
δ-receptor: 82.3 ± 19.8
κ-receptor: 9.7 ± 64.2

SUMMARY

NIH 11084 has high affinity for μ > κ receptors with lower affinity for the δ receptor.

* * *

NIH 11085 (+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan.HCl



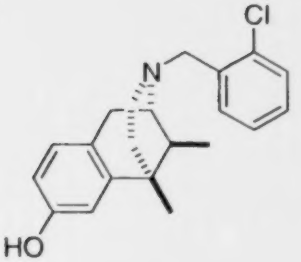
OPIOID RECEPTOR BINDING (μM)

μ receptor: 598 ± 97
δ receptor: >10 (46 ± 4.5% inhibition at 10 μM)
κ receptor: 1476 ± 580

SUMMARY

NIH 11085 has very low affinity for the μ opioid receptor and even lower affinity for κ and δ receptors.

NIH 11088 **(+)-(1*S*,5*S*,9*S*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (nM)

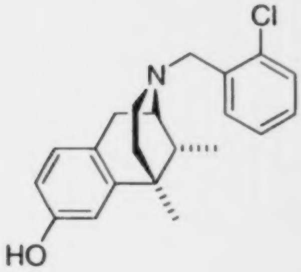
μ receptor: 139 ± 33
δ receptor: 3565 ± 1191
κ receptor: 23.3 ± 2.4

SUMMARY

NIH 11088 has moderate affinity for the κ receptor with 6-fold lower affinity for the μ receptor and extremely low δ receptor affinity.

* * *

NIH 11093 **(-)-(1*R*,5*R*,9*R*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (nM)

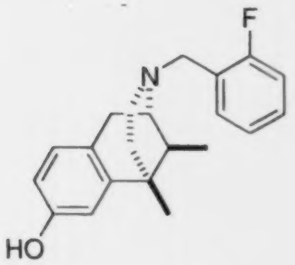
μ receptor: 16.8 ± 2.1
δ receptor: 600 ± 93
κ receptor: 17.5 ± 5.4

SUMMARY

NIH 11093 has equal affinity for μ and κ receptors with lower affinity for the δ receptor.

* * *

NIH 11095 **(+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate**



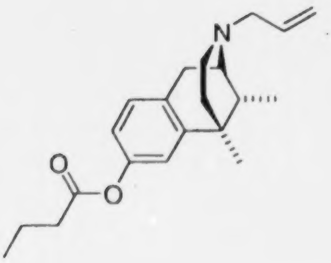
OPIOID RECEPTOR BINDING (nM)

μ receptor: 560 ± 9.2
δ receptor: 4129 ± 867
κ receptor: 47 ± 10.5

SUMMARY

NIH 11095 has affinity for the κ opioid receptor. The compound has 12-fold selectivity for the κ receptor over the μ receptor and 90-fold selectivity for the κ receptor over the δ receptor.

NIH 11096 **(+)-(1*R*,5*R*,9*R*)-2'-Butyroxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl**



OPIOID RECEPTOR BINDING (nM)

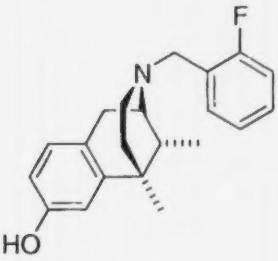
μ receptor: 30.2 ± 13.5
δ receptor: 37.0 ± 1.7
κ receptor: 0.9 ± 0.05

SUMMARY

NIH 11096 has very high affinity for κ, with 30-fold selectivity over μ receptor δ receptors.

* * *

NIH 11097 **(-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan.oxalate**



OPIOID RECEPTOR BINDING (nM)

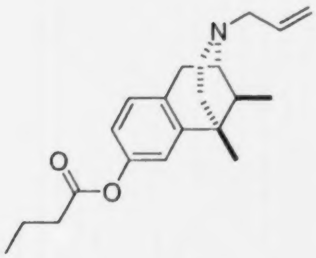
μ receptor: 23.3 ± 4.5
δ receptor: 326 ± 40
κ receptor: 2.1 ± 0.9

SUMMARY

NIH 11097 has high κ receptor affinity with some selectivity over μ receptors (11-fold) and a high selectivity over δ receptors (155-fold).

* * *

NIH 11098 **(+)-(1*S*,5*S*,9*S*)-2'-Butyroxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan.HCl**



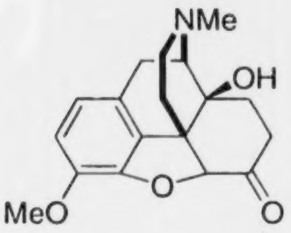
OPIOID RECEPTOR BINDING (nM)

μ receptor: 601 ± 10.8
δ receptor: 3099 ± 405
κ receptor: 1712 ± 167

SUMMARY

11098 has low affinity for all three opioid receptors.

NIH 11107 **Oxycodone.HCl**



OPIOID RECEPTOR BINDING (nM)

μ receptor: 485 ± 134
δ receptor: >3000
κ receptor: >3000

[^{34}S]GTPγS ASSAY (nM)

Agonist activity

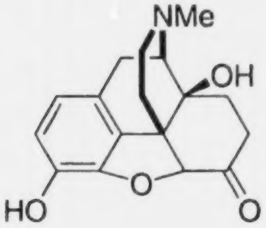
μ-receptor: EC_{50} = 605 ± 82.6 nM (88.2 ± 3.3% stimulation)

SUMMARY

11107 has low affinity for μ opioid receptors. It is an efficacious μ agonist of low potency.

* * *

NIH 11148 **Oxymorphone.HCl**



OPIOID RECEPTOR BINDING (nM)

μ receptor: 8.6 ± 1.8
δ receptor: 50.5 ± 1.2
κ receptor: 93.5 ± 6.4

[^{34}S]GTPγS ASSAY (nM)

Agonist activity

μ-receptor: EC_{50} = 32.2 ± 15.7 nM (91.2 ± 5.6% stimulation)

SUMMARY

NIH 11148 is an efficacious μ agonist and has an affinity for μ opioid receptors > δ > κ, with a low level of selectivity.

* * *

EVALUATION OF NIH 11107 AND 11148 IN RHESUS MONKEYS

Respiratory Effects in Rhesus Monkeys

The effects of NIH 11107 and NIH 11148 on minute volume (Ve), measured for 4 hours following intravenous administration, are shown in figure 1. NIH 11107 produced a dose-related depression of Ve that was approximately

40% of control at a dose of 1 mg/kg. Ve showed moderate recovery over the 3 hr measurement period, and was at approximately 80% of control at this time. NIH 11148 also produced a dose-related suppression of Ve to a maximum of approximately 40% of control at 0.32 mg/kg. Ve had returned to 70% of control levels by approximately 4 hr following intravenous administration of 0.32 mg/kg.

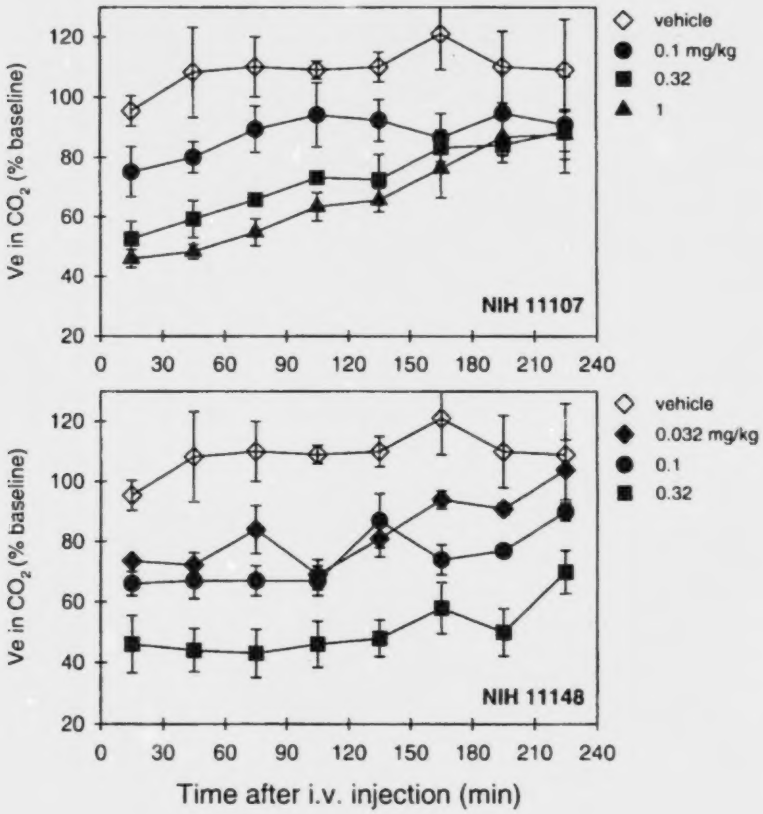


Figure 1

NIH 11107, 1 mg/kg i.v., produced full antinociception against 50°C water for 4 hours in two monkeys.

Reinforcing Effects in Rhesus Monkeys

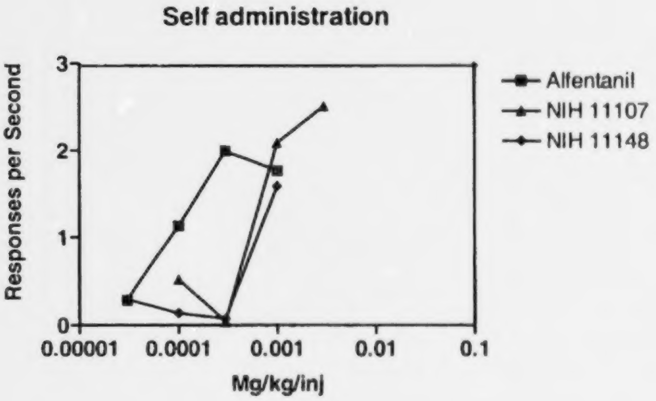


Figure 2

Reinforcing effects of NIH 11107 and 11148 were each studied in rhesus monkeys. Both were found to maintain rates of responding indicative of reinforcing effects (Figure 2). Maximum rates of responding were at least as high as those maintained by alfentanil, the reference compound.

Naltrexone Discrimination in Rhesus Monkeys

Morphine and NIH 11107 were studied in one male (BU; 5.4 kg) and two female (CH and RE; 5.8 and 6.0 kg, respectively) morphine-treated rhesus monkeys. Antagonism of NIH 11107 by 0.032 mg/kg of naltrexone was studied only in the two female monkeys. All drugs were administered s.c.

Subject		Dose (mg/kg) morphine				
	Saline	0.1	0.32	1.0	3.2	5.6
BU	100/1.67	100/1.25	89.1/0.92	50.1/1.13	17.8/1.0	n.t
CH	73.0/1.73	51/7/2.34	42.9/1.84	36.6/2.41	0/2.02	n.t.
RE	100/1.88	100/1.84	96.3/1.79	100/1.53	38.1/1/12	0/1.48

n.t. = not tested

Subject		Dose (mg/kg) NIH 11107		
	Saline	0.32	0.1	0.32
BU	87.5/0.26	77.8/0.58	42.9/1.01	9.1/1.28
CH	79.6/1.61	63.3/1.23	25.2/1.86	0/2.12
RE	100.2.09	91.8/2.53	57.4/1.94	0.1.28

Subject		Dose (mg/kg) NIH 11107				
	0.032 NTX	0.1	0.32	1.0	3.2	5.6
CH	88.2/2.79	86.9/2.69	84.3/1.75	81.8/2.17	0/2.29	n.t.
RE	100/1.86	100/1.40	100/0.94	97.8/1.14	30/1.85	0/1.53

n.t. = not tested

SUMMARY

NIH 11107 is antinociceptive in the monkey tail withdrawal assay. NIH 11107 and NIH 11148 are respiratory drepressants in the monkey with a rapid onset of action following i.v. administration, but NIH 11148 is more potent and longer lasting. NIH 11107 and NIH 11148 act as reinforcers in the monkey with a similar potency that is approximately 10-fold less than alfentanil. In the naltrexone drug discrimination assay NIH 11107 reverses responding in morphine-deprived monkeys and is 10 times more potent than morphine. Naltrexone antagonizes this discriminative stimulus effect of NIH 11107, with 0.032 mg/kg of naltrexone shifting the NIH 11107 dose-effect curve 10-fold rightward. NIH 11107 and NIH 11148 have an in vivo profile in the rhesus monkey consistent with efficacious μ opioid agonism.

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AFFILIATION

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DEPENDENCE STUDIES OF NEW COMPOUNDS IN THE RHESUS MONKEY, RAT AND MOUSE (2002)

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All of the compounds submitted by the Biological Coordinator, Dr. Andrew Coop of the University of Maryland, School of Pharmacy were unknown to us except oxycodone and naltrindole, which were obtained elsewhere. These studies were conducted under the auspices of the Drug Evaluation Committee in association with the College on Problems of Drug Dependence. See summary of new data in Table I.

Dependence-Liability Studies in Rhesus Monkeys

Substitution-for-Morphine (SDS) Test. Male and female rhesus monkeys (M. mulatta) weighing 2.5-7.5 kg were used, and they received 3 mg/kg, s.c., of morphine·SO_4 every 6 hr. All the animals had received morphine for at least 3 months and were maximally dependent on morphine (Seevers and Deneau 1963). A minimal 2-week recuperation period was allowed between tests. At least 3 monkeys/dose were used. The assay (Aceto and co-workers, 1977 and 1978) was initiated by a subcutaneous injection of the test drug or control substances (morphine and vehicle) into animals in a group that had not received morphine for 14-15 hr and showed definite signs of withdrawal. Each animal was randomly chosen to receive one of the following treatments: a) a dose of the compound under investigation; b) morphine control, 3.0 mg/kg; and c) vehicle control, 1 ml/kg. The animals were scored for suppression of withdrawal signs during a 2.5-hr observation period. The observer was "blind" regarding the choice of treatments. At the end of the study, the data were grouped according to dose and drug. The mean cumulative score ± SEM was calculated and the data illustrated in figure form. If indicated, the data were analyzed using the Kruskal-Wallis ANOVA and post hoc Mann-Whitney U-Tests.

Precipitated-Withdrawal (PPT-W) Test. This evaluation was done under the same conditions as described above, except that the animals were administered a test compound 2-3 hr after the last dose of morphine. These animals were not in withdrawal. Naloxone·HCl (0.05 mg/kg, s.c.) served as the positive control.

Primary-Physical-Dependence (PPD) Study. Drug-naive monkeys were medicated with drug, using escalating dose regimens, periodically challenged with naloxone or placed in abrupt withdrawal. They were observed for overt behavioral signs during drug administration and when they were challenged with the antagonist, naloxone, or abruptly withdrawn from the drug.

Rat-Infusion Studies

The continuous-infusion method was reported by Teiger (1974) and certain modifications are indicated as follows. Rats were anesthetized after which each was fitted with a specially prepared cannula which was passed subcutaneously from the nape of the neck to the lateral side of the lower abdomen and then inserted into the peritoneal cavity. The cannula was anchored at both ends with silk sutures and attached to a flow-through swivel mechanism which allowed the animal to move about in the cage and eat and drink normally. The swivel was connected to a syringe which was attached to a syringe pump. The animals received 7-10 ml of solution every 24 hr.

SUMMARY OF NEW DATA

NIH No.	Chemical Name or Generic Class	MOUSE				RAT		MONKEY		
		TF	TFvsM	PPQ	HP	SM	PPD	SDS	PPT-W	PPD
10589	Naltrindole			T[a]						
10967	Tetrahydroisoquinoline	T	T	T[b]	T					
10996	4-Phenylpiperidine	T	T	T[b]	T			T		
11011	6,7-Benzomorphan	T	T	T[b]	T			T		
11012	6,7-Benzomorphan	T	T	T[c]	T			T		
11027	6,7-Benzomorphan	T	T	T	T			T		
11029	6,7-Benzomorphan	T	T	T	T			T		
11030	Butanediol	T	T	T	T			T		
11032	6,7-Benzomorphan	T	T	T	T			T		
11033	6,7-Benzomorphan	T	T	T	T			T		
11036	6,7-Benzomorphan	T	T	T	T			T		
11038	6,7-Benzomorphan	T	T	T	T			T		
11039	6,7-Benzomorphan	T	T	T	T			T		
11040	Phenazocine	T	T	T	T			T		
11041	6,7-Benzomorphan	T	T	T	T			T		
11042	6,7-Benzomorphan	T	T	T	T			T		
11043	6,7-Benzomorphan	T	T	T	T			T		
11044	6,7-Benzomorphan	T	T	T	T			T		
11045	6,7-Benzomorphan	T[d]	T	T	T			T		
11051	6,7-Benzomorphan	T	T	T	T			T		
11052	6,7-Benzomorphan									
11063	4,5-α-Epoxymorphinan	T	T	T	T					
11069	4,5-α-Epoxymorphinan	T	T	T	T					
11070	4,5-α-Epoxymorphinan	T	T	T	T					
11080	6,7-Benzomorphan	T	T	T	T			T		
11081	6,7-Benzomorphan	T	T	T	T					
11082	6,7-Benzomorphan	T	T	T	T					
11083	Diacetoxynaltrexone	T	T[e]	T	T					
11084	Propionylnaltrexone	T	T[f]	T	T					
11085	6,7-Benzomorphan	T	T	T	T					
11093	6,7-Benzomorphan	T	T	T	T					

SUMMARY OF NEW DATA (continued)

NIH No.	Chemical Name or Generic Class	MOUSE				RAT		MONKEY		
		TF	TFvsM	PPQ	HP	SM	PPD	SDS	PPT-W	PPD
11094	Butyrolactone	T	T	T	T					
11095	6,7-Benzomorphan	T	T	T	T					
11096	6,7-Benzomorphan	T	T	T	T					
11097	6,7-Benzomorphan	T	T	T	T					
11098	6,7-Benzomorphan	T	T	T	T					
11107	Oxycodone	T[g,h,i]	T	T	T			T		

T = Test Performed

[a] Special Naltrindole vs ED80 of opioid agonists in PPQ test. [b] Special: Naloxone vs ED80 of NIH 10969 in PPQ test. [c] Special: Naltrindole vs ED80 in PPQ test: [c] Special: Naltrindole vs ED80 of NIH 11012 in PPQ. [d] Special: AD50 of NIH 11045 vs ED80 of endloline. [e] Special: Time course study: NIH 11083 vs ED50 of morphine. [f] Special: AD80 of NIH 11084 vs ED80 of morphine. [g] Special: Naltrindole vs ED80 of NIH 11107 in TF test. [h] Nor-BNI vs ED80 of NIH 11107 in TF test. [i] β-FNA vs ED80 of NIH 11107 in TF test.

Substitution-for-Morphine (SM) Test. The rats received morphine·SO_4 (50 mg/kg/24 hr on the first day, 100 mg/kg/24 hr on the second day, and 200 mg/kg/24 hr from days 3 and 4). Then, a test drug was substituted for 2 days. The morphine controls received an infusion of sterile water for injection. The animals were observed for changes in body weight and for behavioral-withdrawal signs for 0.5 hr at 6, 24, 48, 72 and/or 96 hr after stopping the infusion of morphine.

Primary-Physical-Dependence (PPD) Study. The rats received test compound, as specified above, for 4-6 days and then, were placed in abrupt withdrawal and observed for overt behavioral signs.

Mouse-Antinociception Tests

Male mice, weighing 20-30 g, were used. All drugs were dissolved in distilled water or in the vehicle indicated and injected subcutaneously (s.c.). At least three doses were tested, and 6-10 animals per dose were used. When applicable, ED50's were calculated by using computerized probit analysis. The results obtained with reference compounds are summarized in Table 2. Occasionally, when requested, drugs were given orally (p.o.) or intravenously (i.v.) and the pretreatment times are indicated in the text.

Tail-Flick (TF) and (TF vs M) Assays. The procedure and modifications were described (D'Amour and Smith, 1941 and Dewey et al., 1970 and 1971) in the literature. Briefly, the mouse's tail was placed in a groove which contained a slit under which was located a photoelectric cell. When the heat source of noxious stimulus was turned on, the heat focused on the tail, and the animal responded by flicking its tail out of the groove. Thus, light passed though the slit and activated the photocell which, in turn, stopped the recording timer. The heat source was adjusted to produce tail flick of 2-4 sec under control conditions. Mice were injected with drug or vehicle and tested 20 min later. In three assays for antagonism of the antinociceptive effect, the potential antagonists were administered 10 min before the agonist, and evaluation occurred 20 min later.

Phenylquinone Abdominal-Stretching (PPQ) Assay. The procedure was reported previously (Pearl and Harris, 1966). The mice were injected with test drug and 10 min later received 2.0 mg/kg intraperitoneally (i.p.) of a freshly prepared paraphenylquinone (PPQ) solution. The mice were then placed in cages in groups of two each. Ten min after the PPQ injection, the total number of stretches per group were counted over a 1-min period. A stretch was characterized by an elongation of the mouse's body, development of tension in the abdominal muscles, and extension of the forelimbs. The antinociceptive response was expressed as the percent inhibition of the PPQ-induced stretching response.

Hot-Plate (HP) Assay. The method was also reported previously (Eddy and Leimbach, 1953 and Atwell and Jacobson, 1978). The hot plate was held at 55°C. Mice were placed on the hot plate and activity was scored if the animal jumped or licked its paws after a delay of 5 sec or more, but no more than 30 sec beyond the control time.

Table 2

Comparative Data (ED50 or AD50, mg/kg s.c.) [95% C.L.] of Selected Standards in 4 Mouse Agonist-Antagonist Tests

Drug	Tail-Flick	Tail-Flick Antagonist	Phenylquinone	Hot-Plate
Pentazocine	15% at 10.0	18 (12-26) (1.0-2.5)	1.7	13% at 30.0
Cyclazocine	17% at 1.0[a]	0.03 (0.02-0.78)	0.01 (0.005-0.03)	25% at 9.0
Nalorphine·HCl	None at 10.0	2.6 (0.7-1.0)	0.6 (0.03-1.44)	13% at 30.0
Naloxone·HCl	None at 10.0	0.04 (0.0-0.09)	No Activity	- - - -
Naltrexone·HCl	None at 10.0	0.007 (.002-0.02)	No Activity	- - - -
Morphine·$S0_4$[b]	1.92 (0.89-4.14)	Inactive	0.4[b] (0.2-0.8)	0.85 (0.39-1.86)
Codeine·$P0_4$	- - - -	Inactive	8.25 (5.12-13.29)	6.4 (2.4-16.8)
Meperidine·HCl	8.37 (4.59-15.27)	Inactive	- - - -	4.6 (1.18-11.7)

[a] Mice were ataxic at 3.0 and 10.0 mg/kg but there was no further increase in reaction time

[b] ICR - Harlan-Sprague-Dawley Inc.

Calculation of Apparent pA2 . Using the tail-flick or PPQ assay, the apparent pA_2 and 95% confidence limits were calculated using Schild and constrained plots as described in Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 2nd ed., Springer Verlag, NY., 1987).

Briefly, mice were pretreated with vehicle or various doses of antagonist followed 10 min later by an injection of agonist. The mice were tested 30 min after receiving the antagonist. Dose-response lines for antinociception were plotted using at least 3 doses of each opioid agonist in the presence of vehicle or one of the selected doses of antagonist. ED5Os were estimated according to the method of Litchfield and Wilcoxon (J. Pharmacol. Exp. Ther., 96, 399, 1949). Each dose ratio (x) was calculated by dividing the ED50 of the opioid in the presence of a given dose of antagonist by that of the agonist alone. Log (x-l) was plotted against the negative logarithm of the molar dose of the antagonist. At least 3 logs (x-l) were plotted. The pA_2 values for the antagonists were calculated from the point of intersection of the regression line with the abscissa. See Table 3 for summary of results.

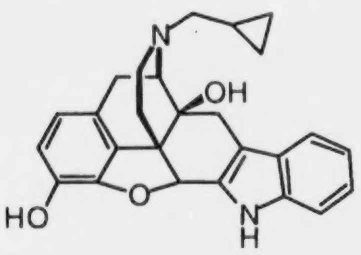
Table 3. Apparent pA_2 values[a] using the mouse tail-flick assay

Treatment Antagonist/Agonist	Schild Plot pA_2 (95% C.L.) Slope	Constrained Plot pA_2(95% C.L.)
1) Naloxone/Morphine	7.2 (7.0-7.4)-1.2	7.3 (7.1 - 7.6)
2) Naloxone/Sufentanil	7.0 (6.5 - 7.5)-1.0	7.0 (6.8 - 7.1)
3) Naloxone/Mirfentanil	7.6 (7.3 - 8.0)-0.7	7.2 (6.9 - 7.5)
4) Naloxone/NIH 10672 (Enadoline) (selective kappa agonist)	6.1 (5.6 - 6.6)-1.2	6.6 (6.3 - 7.0)
5) Naloxone/U-50,488 (kappa agonist)	6.6 (6.3 - 6.9)-1.1	6.2 (5.9 - 7.3)
6) Naloxone/(-)-Nicotine	5.3 (5.3-5.3)-0.5	-
7) Nalmefene/Morphine	8.0 (7.6 - 8.3)-1.1	8.0 (7.7 - 7.6)
8) Naltrexone/Morphine	7.7 (4.9 - 10.5)-0.8	7.6 (7.1 - 8.3)
9) (-)-Quadazocine/Morphine	6.8 (6.7 - 7.0)-0.9	6.8 (6.1 - 7.6)
10) (-)-Quadazocine/Enadoline	6.2 (6.1 - 6.2)-1.7	6.7 (6.6 - 6.8)
11) nor BNI/Enadoline	6.5 (5.9 - 7.0)-1.3	6.6 (5.9 - 7.3)
12) Mecamylamine/(-)-Nicotine	6.6 (6.2 - 6.9)-0.9	-

[a] Negative logarithm of the molar concentrations of antagonist required to produce a two-fold shift of the agonist dose-response curve to the right. Competitive antagonism can be assumed when slope = -1. pA_2 provides a measure of the relative potency and affinity of the antagonist. When the slope differs significantly from unity, this may indicate non-equilibrium conditions, interactions with multireceptors, receptor sensitization, precoupling mechanisms, or multiple drug properties. With a constrained plot, the slope of the regression line is restricted to slope of - 1.

Special Intracerebroventricular Tail-Flick and PPQ Assays. In order to develop an in-vivo agonist and antagonist model to correlate with the in-vitro binding data of the various opioid receptor types (mu, kappa and delta), we chose the mouse Tail-Flick and PPQ tests and a variety of routes of administration. The intracerebroventricular (i.c.v.) route was chosen to accommodate the fact that no delta agonist is available which is active by peripheral routes of administration.

NIH 10589 Naltrindole·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF - Inactive at 1, 10 and 30*
2) TF vs. M - Inactive at 1, 20 and 30*
3) PPQ - 0% at 1,and 10 and 28% at 30*
4) HP - Not tested

*Previously reported, see NIDA Res. Monog. 95, 614, 1989

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NIH 10589 (continued)

NEW DATA

Table 1. The interaction of opioid-agonist subtypes and naltrindole in the mouse PPQ test.

Antagonist	Antagonist Pretreatment Time (min)	Agonist ED_{80}	Agonist Pretreatment Time (min)	AD_{50} (95% Confidence Limits)
Naltrindole (s.c.)	30	Morphine Sulfate (mu agonist) (s.c.)	20	30.0 mg/kg: 7% antagonism 10.0 mg/kg: 7% antagonism 1.0 mg/kg: 7% antagonism
Naltrindole (s.c.)	30	NIH 10672 (Enadoline) (kappa agonist) (s.c.)	20	30.0 mg/kg: 0% antagonism 10.0 mg/kg: 0% antagonism 1.0 mg/kg: 0% antagonism
Naltrindole (s.c.)	30	U-50,488 ED_{80} (kappa agonist) (s.c.)	20	30.0 mg/kg: 29% antagonism 10.0 mg/kg: 8% antagonism 1.0 mg/kg: 0% antagonism
Naltrindole (s.c.)	30	DPDPE delta agonist (i.c.v.)	10	AD_{50} = 0.12 mg/kg (0.1 - 0.27) Slope - 3.63

MONKEY DATA (Previously reported, see NIDA Res. Monog. 95, 615, 1989
(SDS)

This compound did not substitute for morphine. It exacerbated withdrawal at 3 and 12 mg/kg (see fig NIH 10589).

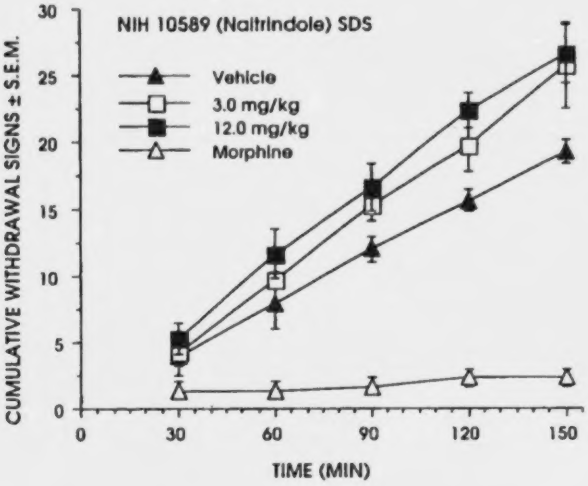
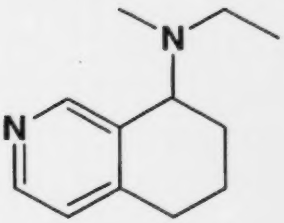


Fig NIH 10589 Results of study in which single doses of NIH 10589 (Naltrindole) were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Naltrindole is a selective delta opioid antagonist in the PPQ test. Note however, that the drug also acts as a mu antagonist in the morphine-dependent monkey or perhaps reveals a delta component of withdrawal.

NIH 10967 8-(Ethylmethylamino)-5,6,7,8-tetrahydroisoquinoline



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – 0.8 (0.64 – 1.01)[a]
2) TF vs. M – Inactive at 1, 10 and 30[b]
3) PPQ – 0.37 (0.13 – 1.06)
4) HP – 0.8 (0.3 – 2.1)[c]

[a] 2 of 6 convulsed and died at 1 mg/kg and 1 of 6 convulsed but did not die at 1 mg/kg.
[b] All convulsed and died at 10 and 30 mg/kg
[c] All convulsed and died at 10 mg/kg and 4 of 8died at 3 mg/kg.

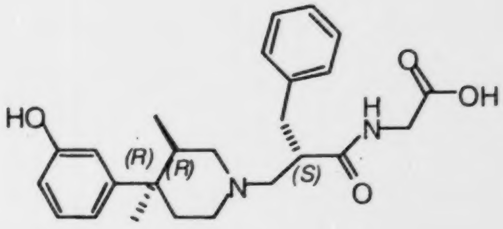
Special: Naloxone vs NIH 10967 ED$_{80}$ in PPQ test = 0% antagonism.

MONKEY DATA
(SDS)

Not tested.

Comment: The compound displayed potent antinociceptive effects. However, the drug also produced convulsions and was lethal. The profile of activity does not indicate opioid properties.

NIH 10996 (+)-2-[2(*S*)-Benzyl-3-[4(*R*)-(3-hydroxphenyl)-3(*R*),4-dimethylpiperidin 1-yl]propionamido]acetic acid



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) aTF (s.c.) – Inactive at 1, 10 and 30[a]
   bTF (oral) - 3% at 1, 0% at 10 and 1% at 30[a,b]
   cTF (oral) - 0% at 1, 1% at 10 and 12% at 30[a,c]

(Repeat)

1) [a]TF (s.c.) - Inactive at 1, 10 and 30 (in 50% DMSO)[d]
   [b]TF vs. M – Inactive at 1, 10 and 30[a]
   [c]TF vs M – 26 % at 1, 0% at 10 and 21% at 30 (in 50% DMSO)[d]
2) PPQ – 0% at 1, 3% at 10, 43% at 30 and 69% at 60[a]
3) HP – Inactive at 1, 10 and 30[a]

[a] Vehicle was 30% hydroxypropyl-β-cyclodextrin in water.
[b] Twenty min pretreatment.
[c] Sixty min pretreatment.
[d] DMSO is dimethyl sulfoxide.

Special test: Naloxone (s.c.) vs 69% activity at 60 mg/kg of NIH 10996 (s.c.) in the PPQ test: Inactive at 1 and 10 mg/kg.

NIH 10996 (Continued)

MONKEY DATA
(SDS

At 5 and 20 mg/kg, NIH 10996 neither substituted for morphine nor exacerbated withdrawal. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

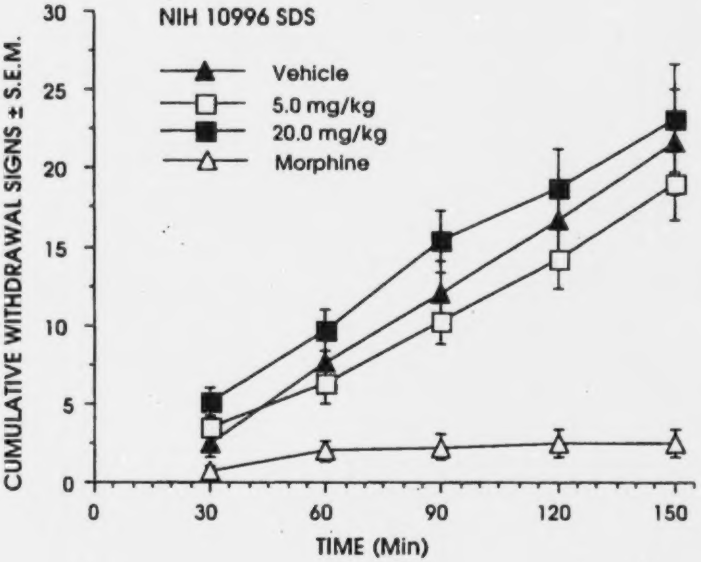
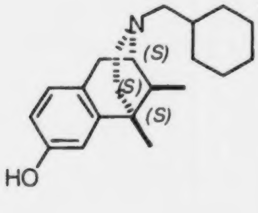


Fig NIH 10996-SDS. Results of study in which single doses of NIH 10996 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: When given subcutaneously or orally, NIH 10996 did not display remarkable antinociceptive properties in a variety of tests when given in different vehicles (30% hydroxypropyl-β-cyclodextrin in water or 50% dimethylsulfoxide aqueous solution). The effects in mice or monkeys were not indicative of mu-opioid activity.

NIH 11011 (+)-(1*S*,5*S*,9*S*)-2-(Cyclohexylmethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – Inactive at 1, 10 and 30
2) TF vs. M – 20% at 1, 1% at 10 and 7% at 30
3) PPQ – 17.57 (5.91 – 52.26)
4) HP – 0% at 1 and 10, 13% at 30

NIH 11011 (continued)

Special Test:

Natrindole vs NIH 11011, 60 mg/kg, in PPQ Test: Antagonism = 23% at 1, 33% at 3, 11% at 10 and 0% at 30.

MONKEY DATA
(SDS)

Attenuation of withdrawal signs at 16 mg/kg was accompanied by jaw sag and ataxia. These behavioral signs and salivation were also noted at the lower dose.

Drug supply was exhausted. Thus, a complete evaluation of NIH 11011 was precluded.

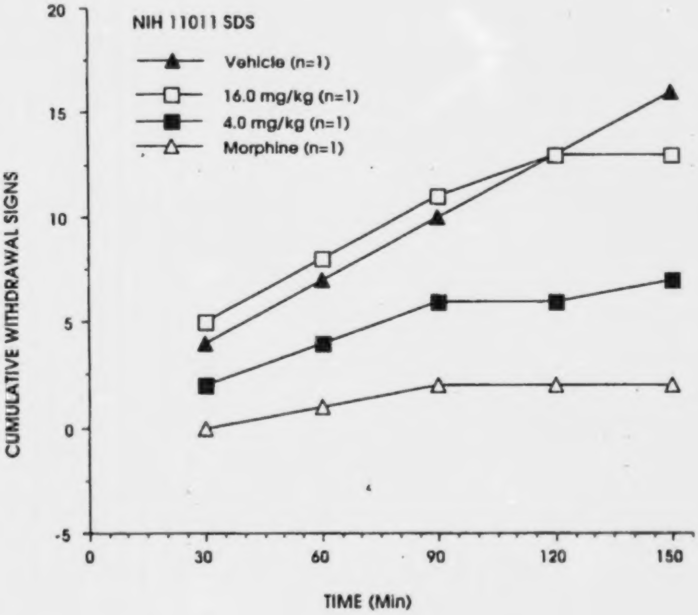
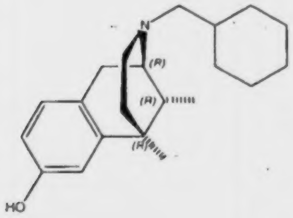


Fig NIH 11011-SDS. Results of study in which single doses of NIH 11011 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity does not suggest mu opioid-receptor interactions.

NIH 11012 (-)-(1R,5R*S*,9*R*-2-(Cyclohexylmethyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – 3% at 1 and 10, 0% at 30[a]
2) TF vs. M – 3.70 (1.02 – 13.45)[a]
3) PPQ – 14.62 (3.12 – 68.3)[a,b]
4 HP – 0% at 1 and 10, 13% at 30[a]

[a] Vehicle was 4% Tween 80 in water.

[b] One mouse at 60 mg/kg was very lethargic and one mouse had convulsions that lasted to end of experiment.

Special Test:

5) Naltrindole (s.c.), (30 min pretreatment) vs NIH 11012 ED80 in the PPQ test: 15% at 1, and 13% at 10 and 30[c] mg/kg.

[c] Vehicle was 5% hydroxypropyl-β-cyclodextrin in water.

MONKEY DATA
(SDS)

At doses of 0.75 and 3.0 mg/kg, NIH 11012 did not substitute for morphine or exacerbate withdrawal. Jaw sag was noted at 3 mg/kg. One monkey who received 12 mg/kg had tremors followed by convulsions. Pentobarbital (30 mg/kg, i.p.) effectively terminated the convulsions.

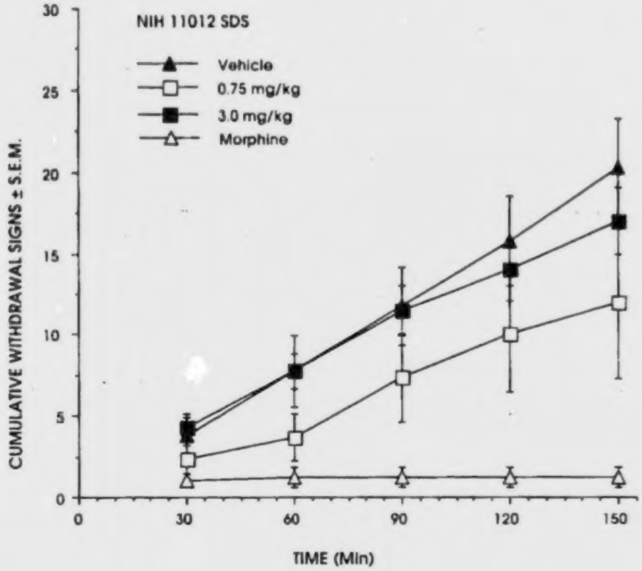


Fig NIH 11012-SDS. Results of study in which single doses of NIH 11012 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results suggest that NIH 11012 has weak mu-opioid antagonist properties. Some antinociception was noted in the PPQ test which was not delta-opioid receptor related. The drug also produced convulsions in both species.

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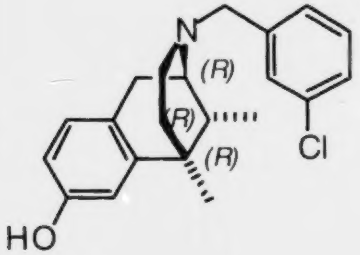
NIH 11027 (-)-(1*R*,5*R*,9*R*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – Inactive at 1, 10 and 30[a]
2) TF vs. M – 2% at 1, 0% at 10 and 21% at 30[a]
3) PPQ – 15% at 1 and 0% at 10 and 30[a]
4) HP – 0% at 1 and 10, 25% at 30[a]

[a] Vehicle was dilute lactic acid + heat.

MONKEY DATA
(SDS)

Doses of 4 and 16 mg/kg of NIH 11027 exacerbated withdrawal in morphine-dependent monkeys (see figure). The effect was not dose related and duration was at least 2 1/2 hr. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

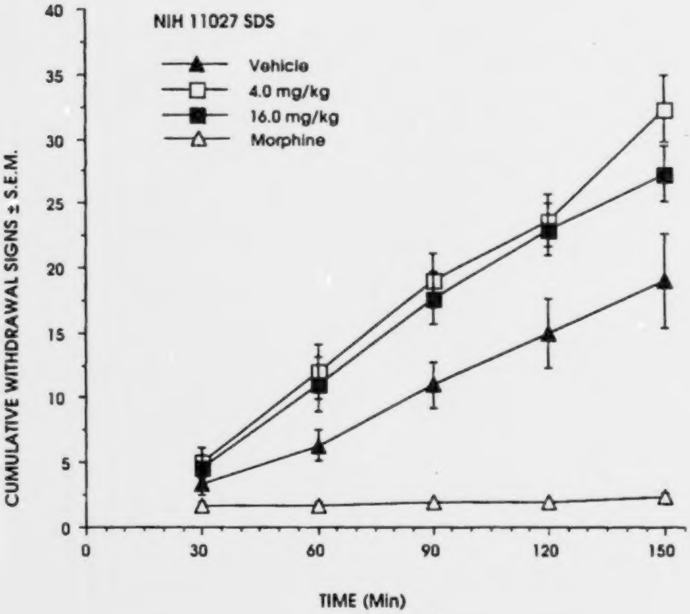
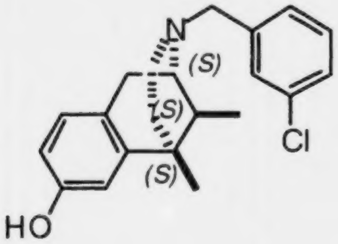


Fig NIH 11027-SDS. Results of study in which single doses of NIH 11027 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11027 may have weak mu-opioid receptor antagonist properties.

NIH 11029 (+)-(1*S*,5*S*,9*S*)-2-(3-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – 2.1% at 1, 0% at 10 and 21.5% at 30*
2) TF vs. M – Inactive at 1 and 10, 6% at 30*
3) PPQ – Inactive at 1 and 10, 44% at 30*
4) HP – 13% at 1, Inactive at 10 and 30*

*Vehicle was dilute lactic acid in water.

MONKEY DATA
(SDS)

At 4 and 16 mg/kg, some partial attenuation of withdrawal signs was observed (see figure). The effect was not dose related. Jaw sag was noted in one monkey at the high dose. The drug acted promptly. Duration of action was 2 1/2 hr. Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

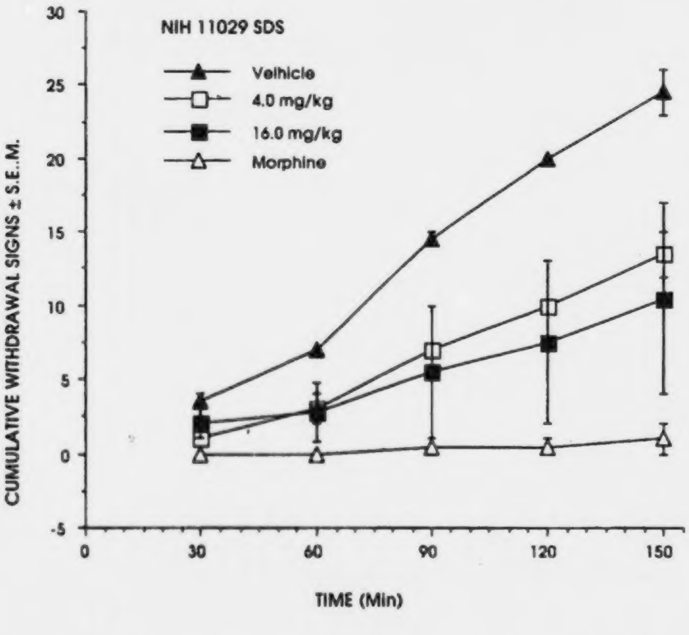
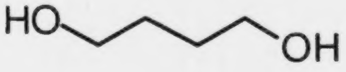


Fig NIH 11029-SDS. Results of study in which single doses of NIH 11029 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity does not indicate significant opioid effects.

NIH 11030 1,4-Butanediol (Purported precursor of γ-hydroxybutyrate)



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1)a TF – Inactive at 1, 10% at 10 and 45% at 30[a]
b TF – Inactive at 1, 3% at 10 and 6% at 30[b]
2)a TF vs. M – Inactive at 1 and 10, 20% at 30[b]
b TF vs. M – 5% at 1, 11% at 10 and 6% at 30[b]
3)a PPQ – 8% at 1, 10% at 10 and 40% at 30[b]
b PPQ – Inactive at 1, 17% at 10 and 23% at 30[b]
4)a HP – Inactive at 1, 10 and 30[a]
b HP – 13% at1, Inactive at 10 and 30[b]

[a] Pretreatment time 20 min.
[b] Pretreatment time 60 min.

MONKEY DATA
(SDS)

NIH 11030 neither substituted for morphine nor exacerbated withdrawal in the dose range of 4.5 to 18 mg/kg. Curiously, it attenuated withdrawal signs at the low dose but not at the higher dose.

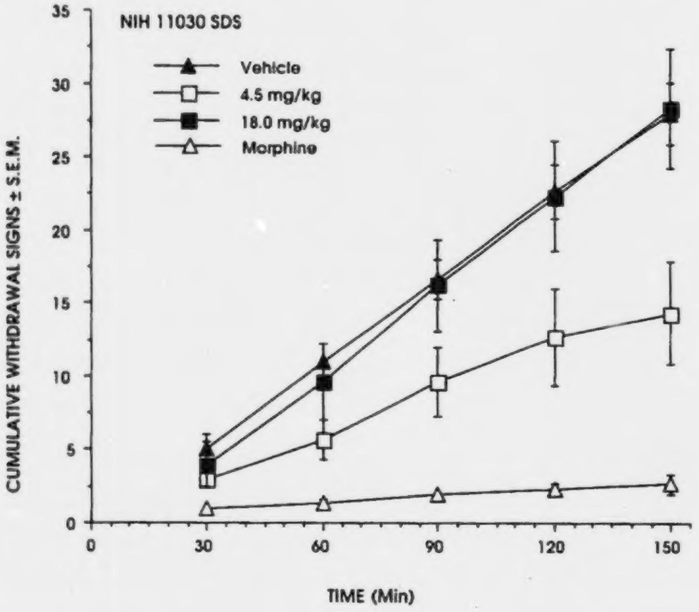


Fig NIH 11030-SDS. Results of study in which single doses of NIH 11030 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Apparently, this compound is free of opioid effects.

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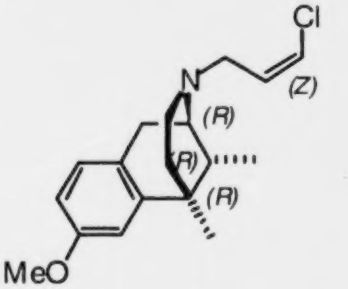
NIH 11032 (-)-(1*R*,5*R*,9*R*)-2-(3-cis-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan Oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – 3% at 1, 13% at 10 and 14% at 30
2) TF vs. M – 1.08 (0.31 - 3.73)
3) PPQ – 17.43 (10.26 - 29.62)

Vehicle was water aided by warming.

MONKEY DATA
(SDS)

NIH 11032 did not substitute for morphine and may have exacerbated withdrawal. Because the vehicle controls showed fewer than the usual number of withdrawal signs, the exacerbation of withdrawal depicted in the figure may be exaggerated. The drug does produce some jaw sag and slowing in 1/3 at 1.25 mg/kg and jaw sag in 2/3, slowing in 2/3 and body sag in 1/3 monkeys at 5 mg/kg. Vehicle was 10% aqueous hydroxypropyl-β-cyclodextrin solution.

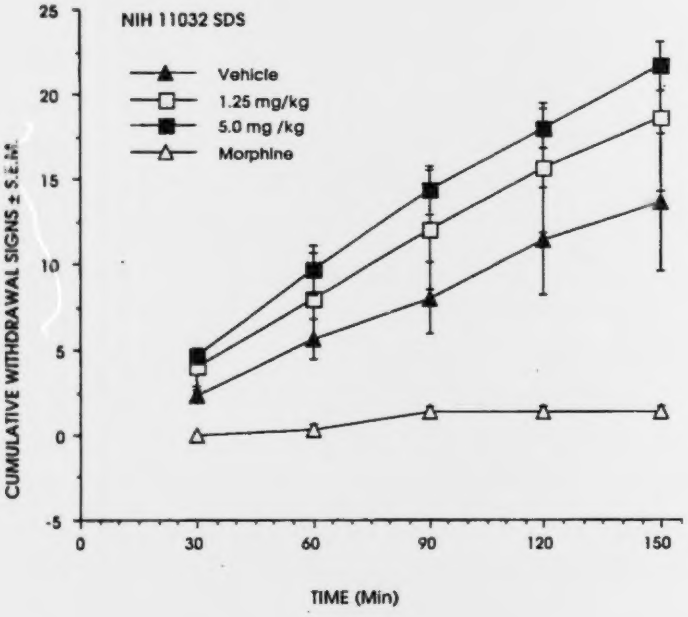
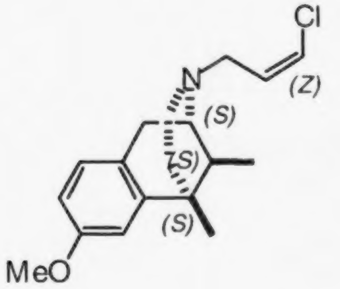


Fig NIH 11032 SDS. Results of study in which single doses of NIH 11032 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: NIH 11032 has very weak mu-opioid receptor antagonist activity as well as some antinociceptive action.

NIH 11033 (+)-(1*S*,5*S*,9*S*)-2-(3-cis-Chloro-2-propenyl)-5,9-dimethyl-2'-methoxy-6,7-benzomorphan oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – Inactive at 1, 10 and 30
2) TF vs. M – 32% at 1, 15% at 10 and 47% at 30
3) PPQ – Inactive at 1 and 10, 16% at 30
4) HP – 25% at 1, 0% at 10 and 13% at 30

MONKEY DATA
(SDS)

As shown in the accompanying figure, NIH 11033 did not produce a remarkable attenuation of withdrawal signs. At the high dose slowing, ataxia and jaw sag were noted.

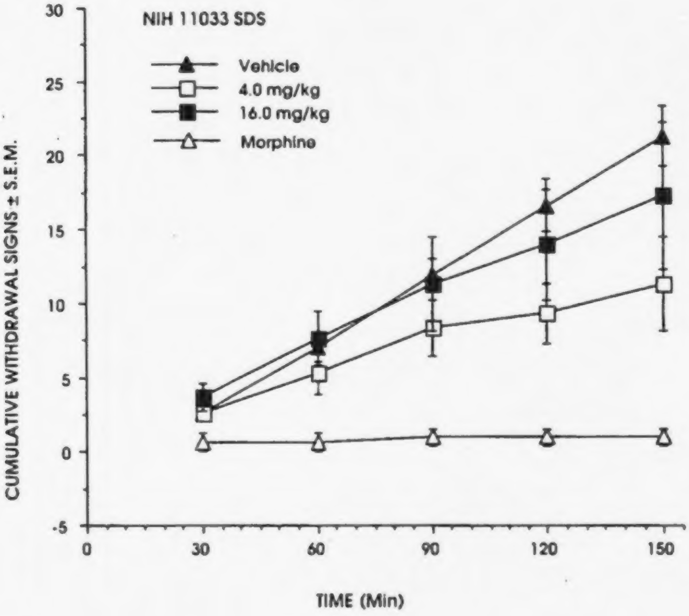
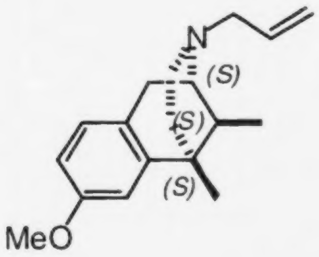


Fig NIH 11033-SDS. Results of study in which single doses of NIH 11033 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: Very weak biological activity in the mouse as well as non dose-related attenuation of withdrawal signs in the monkey, suggest that NIH 11033 does not have remarkable mu-opioid properties.

NIH 11036 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan Oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – 4% at 1, 5% at 10 and 0% at 30
2) TF vs. M – Inactive at 1, 10 and 30
3) PPQ – 21.6 (12.7 - 36.5)
4) HP - Inactive at 1, 10 and 30
5) TF -5% at 1 and 5, 25% and 31% at 10 and 12% at 30[c] (Intravenously)

[c] Tremors at 10 mg/kg and clonic convulsions, rapid respiration at 30. 1/6 Straub tail and 1/6 died at 30.

MONKEY DATA
(SDS)

At doses of 4.5 and 18 mg/kg, NIH 11036 neither substituted for morphine nor exacerbated withdrawal (see figure). At the low dose, overt behavioral signs designated as slowing (1/3) and ataxia (2/3) were noted. At the higher dose, slowing (2/3), ataxia (2/3), jaw sag 1/3), eyelid ptosis (2/3) and glassy eyes (1/3) were observed.

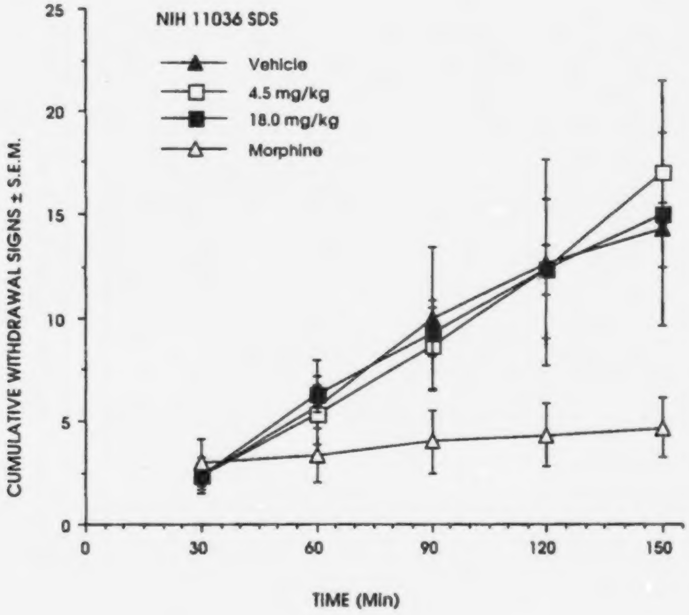
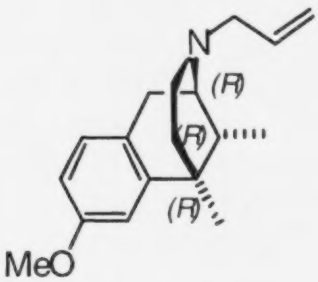


Fig NIH 11036-SDS. Results of study in which single doses of NIH 11036 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity in mice and monkeys is not indicative of mu-opioid agonist activity. However, the the drug has significant central nervous system depressant activity.

NIH 11038 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-methoxy-2-(2-propenyl)-6,7-benzomorphan Oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – Inactive at 1, 10 and 30
2) TF vs. M – 3.25 (1.05 -10.04)[a]
   TF vs. M – 9.09 (1.97 - 41.98)[b]
3) PPQ – Inactive at 3, 24% at 10, 3% at 20 and
   8% at 30
4) HP – Inactive at 30

[a]30-min pretreatment time.
[b]4-hr pretreatment time.

MONKEY DATA
(SDS)

At 2 mg/kg, NIH 11038 exacerbated withdrawal (see figure). Onset was prompt and duration of action was at least 2 1/2 hr. Also noted, at 2 mg/kg was slowing in 3/4 and ataxia in 2/4 of the subjects. At 8 mg/kg, the signs slowing in 3/4, ataxia in 3/4, jaw sag in 2/4 and eyelid ptosis in 1/4 of the monkeys were observed during the first 90 min of the study.

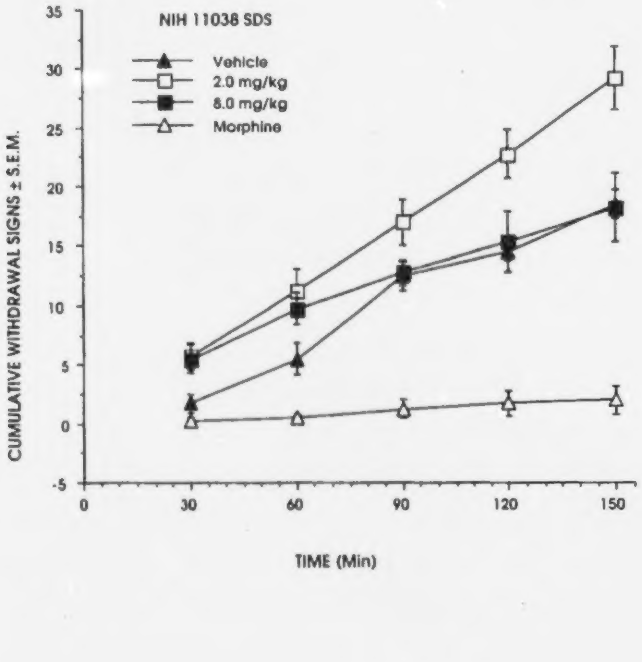
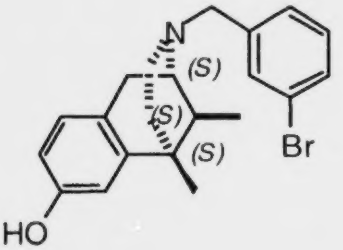


Fig NIH 11038-SDS. Results of study in which single doses of NIH 11038 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The results indicate that NIH 111038 is a weak mu-opioid receptor antagonist. Some of the behavioral signs noted suggest other CNS effects.

NIH 11039 (+)-(1*S*,5*S*,9*S*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – 12% at 1, 1% at 10 and 5% at 30
2) TF vs. M – 6% at 1, 21% at 10 and 19% at 30
3) PPQ – 30% at 1, 37% at 10 and 47% at 30
4) HP – Inactive at 1 and 10, 13% at 30

MONKEY DATA
(SDS)

At doses of 4 and 16 mg/kg, NIH 11039 did not display mu-opioid agonist or antagonist action in morphine-dependent rhesus monkeys.

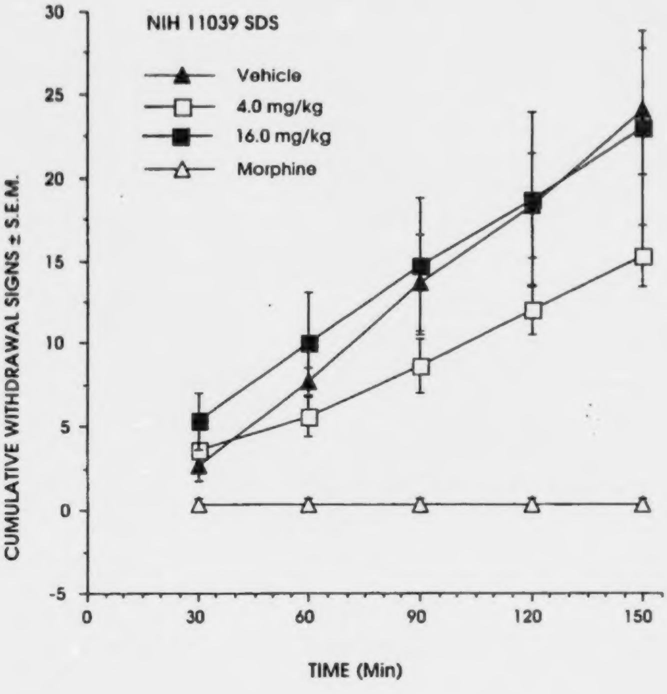
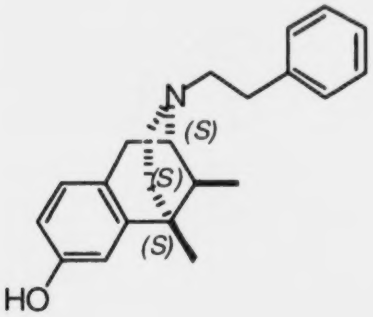


Fig NIH 11039-SDS. Results of study in which single doses of NIH 11039 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: NIH 11039 does not display activity typical of mu-opioid agonists or antagonists.

NIH 11040 (+)-Phenazocine Hydrobromide (NIH 7614)



MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – 0% at 1, 24% at 10 and 15% at 30.
2) TF vs. M – 2% at 1, 0% at 10 and 13% at 30.
3) PPQ – 3.4 (1.4 - 8.2).
4) HP - 0% at 1, 25% at 10 and 38% at 30.[a,b]

[a] Vehicle was 5% hydroxypropyl-β-cyclodextrin in H_2O.
[b] Lightly sedated at 30 mg/kg.

MONKEY DATA
(SDS)

At doses of 1, 4 and 16 mg/kg, NIH 11041 neither substituted for morphine nor exacerbated withdrawal in morphine-dependent monkeys (see figure). Jaw sag was observed at the lowest dose in one monkey, slowing and eyelid ptosis were noted in 1/3 at the next higher dose, and jaw sag, ataxia, slowing, vomiting and convulsions were noticed in one of two monkeys at the highest dose. Pentobarbital, 30 mg i.p., promptly terminated the convulsions. Drug supply was exhausted. Vehicle was 10% hydroxypropyl-β- cyclodextrin in water.

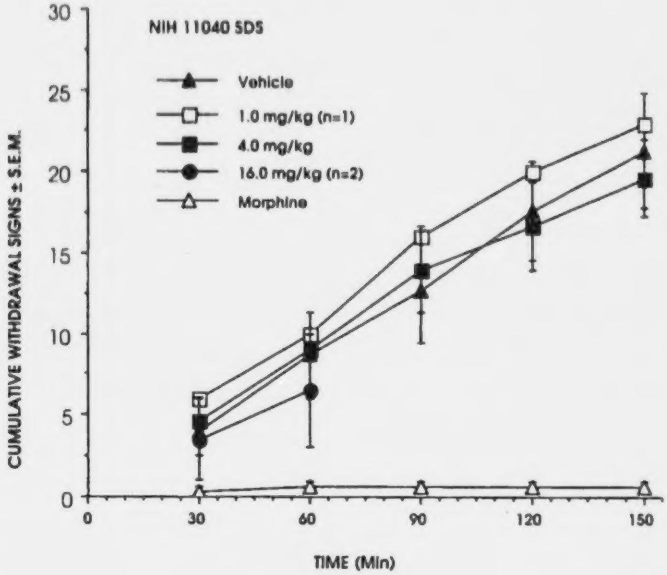
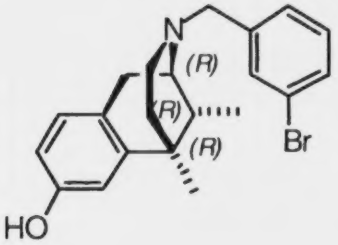


Fig NIH 11040 SDS. Results of study in which single doses of NIH 11040 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The profile of activity exhibited by NIH 11040 does not portend remarkable mu-opioid properties. Antinociceptive activity in the PPQ test coupled with convulsions in the SDS study hint at delta-opioid activity.

NIH 11041 (-)-(1*R*,5*R*,9*R*)-2-(3-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – 3% at 1 and inactive at 10 and 30.[a]
2) TF vs. M – Inactive at 1, 10 and 30.[a]
3) PPQ – 18% at 1, 0% at 10 and 18% at 30.[a]
4) HP - Inactive at 1, 10 and 30.[a]

[a] Vehicle was 10% hydroxypropyl-β-cyclodextrin in H_2O.

MONKEY DATA
(SDS)

At doses of 4 and 16 mg/kg NIH 11041 was without apparent effect in withdrawn morphine-dependent rhesus monkeys. The results are depicted in the accompanying figure.

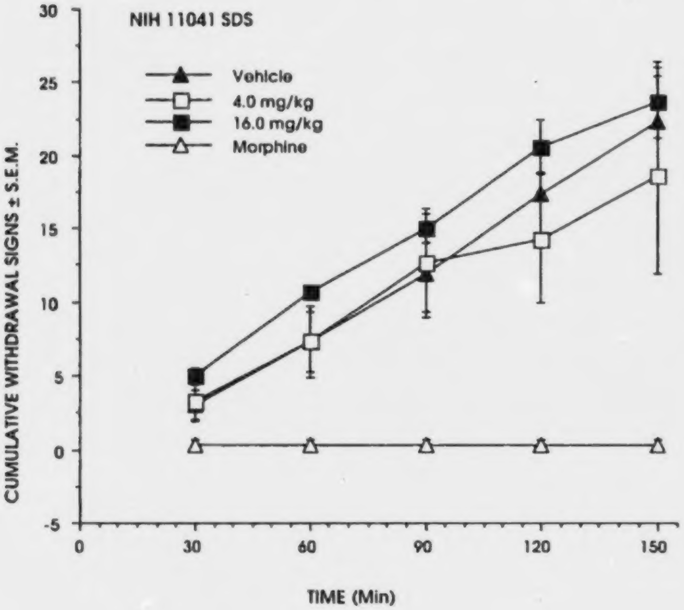


Fig NIH 11041 SDS. Results of study in which single doses of NIH 11041 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: NIH 111041 appeared devoid of opioid activity in mice and morphine-dependent monkeys.

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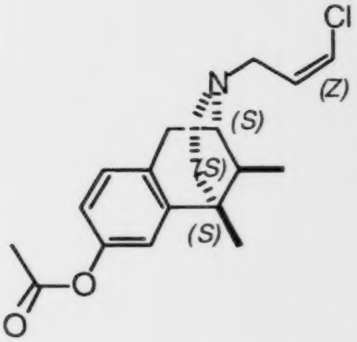
NIH 11042 (+)-(1*S*,5*S*,9*S*)-2'-Acetoxy-2-(3-*cis*-Chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan Oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – 0% at 1, 6% at 10 and 0% at 30.
2) TF vs. M – 22.0 (13.6 - 35.6).
3) PPQ – 3% at 1, 26% at 10 and 35% at 30[a,b,c]
4) HP - 13% at 1 and 0% at 10 and 30.[a,c]

[a] Ataxic at 30.
[b] Slightly ataxic at 20.
[c] Hyperactivity at 30.

MONKEY DATA
(SDS)

NIH 11042 did not substitute for morphine or exacerbate withdrawal (see figure). Attenuation of withdrawal signs was probably associated with the side effects of the drug which were: ataxia in 3/4, slowing in 4/4, jaw sag in 1/4 at 1 mg/kg; body sag in 1/4 and eyelid ptosis in 1/4 at 4 mg/kg; and, ataxia in 2/2 and slowing in 2/2 at highest dose.

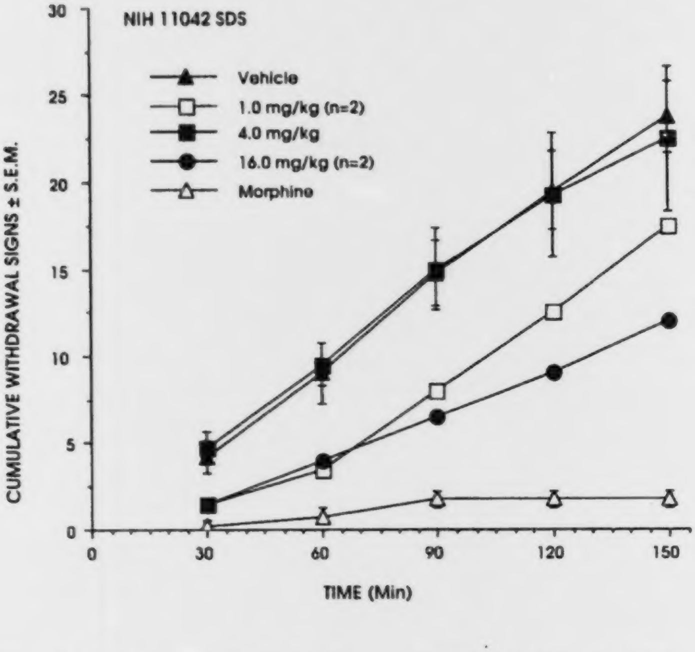
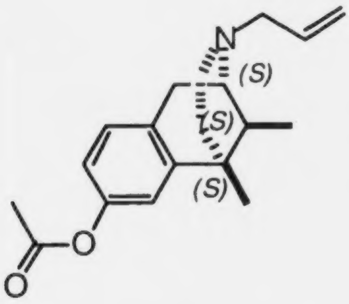


Fig NIH 11042 SDS. Results of study in which single doses of NIH 11042 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: The results in mice indicate that NIH 11042 has very weak mu-antagonist properties and potent CNS effects.

NIH 11043 (+)-(1*S*,5*S*,9*S*)-2'-Acetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan Oxalate



MOUSE DATA - ED50 OR AD50
(95% C.L.) mg/kg or % change

1) TF – Inactive at 1, 10 and 30.[a,b]
2) TF vs. M – Inactive at 1, 10 and 30.
3) PPQ – 8.90 (5.08 - 15.60).
4) HP - 13% at 1 and 0% at 10 and 30.[a]

[a] Jumpy when handled.
[b] Ataxia at 30.

MONKEY DATA
(SDS)

Although NIH 11043 appeared to attenuate withdrawal signs in rhesus monkeys in a dose-related manner (see accompanying figure), the reduction in signs was probably associated with the severe side effects of the drug. At the high dose, 4/4 were severely ataxic, 4/4 were slow, 3/4 had jaw sag, 2/4 had eyelid ptosis and 1/4 developed body sag. The drug acted promptly and its effects lasted for approximately 90 min.

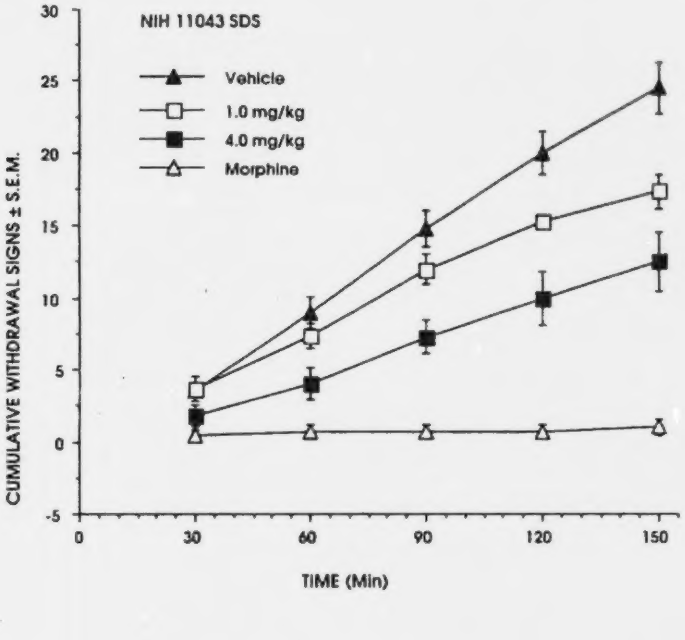
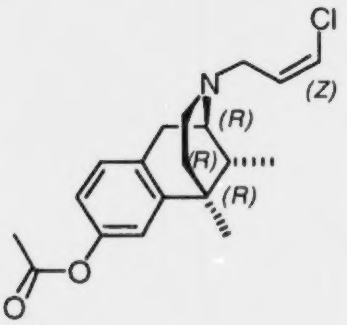


Fig NIH 11043 SDS. Results of study in which single doses of NIH 11043 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: In the mouse and rhesus monkey, NIH 11043 did not display mu-opioid receptor agonist or antagonist properties. Prominent CNS effects were noted.

NIH 11044 (-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-2-(3-cis-Chloro-2-propenyl)-5,9-dimethyl-6,7-benzomorphan Oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

5) TF – Inactive at 1, 10 and 30 [a,b]
6) TF vs. M - 0.24 (0.01 - 0.60)
3) PPQ – 10.50 (2.42 - 45.60)[a]
7) HP - 25% at 1, 0% at 10 and 30[a]

[a] Ataxia at 10 and 30.
[b] Increased locomotor activity at 10.

MONKEY DATA
(SDS)

The behavioral signs exhibited by NIH 11044 suggested multiple opioid properties. The signs designated jaw sag, slowing, eyelid ptosis, vomiting and, especially salivation, suggested kappa-opioid agonist properties. Also observed, were the signs designated retching, vomiting, tremors, and rigid abdominal muscles accompanied by vocalization when palpated, indicative of mu-opioid receptor antagonist activity. It should be noted that vomiting is noted infrequently in abruptly withdrawn morphine-dependent monkeys. This sign is usually associated with precipitated withdrawal. These effects were dose-related, of rapid onset and were diminished after 90 min. At 1 mg/kg, the drug appeared to exacerbate withdrawal. At the highest dose (10 mg/kg), the results depicted in the accompanying figure suggest that this compound was attenuating withdrawal. However, this interpretation is probably not correct because all the monkeys receiving this dose refused to leave the pen to have their abdomens palpated during the 30-min check. Two would not leave the pen during the 60-min examination and 1 declined the 90-min check. The end result was a lower than normal cumulative withdrawal score.

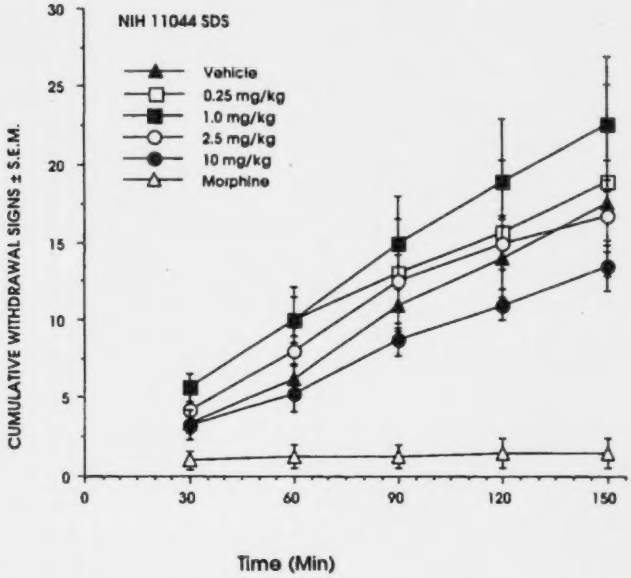


Fig NIH 11044 SDS. Results of study in which single doses of NIH 11044 were substituted for morphine in morphine-dependent monkeys in withdrawal

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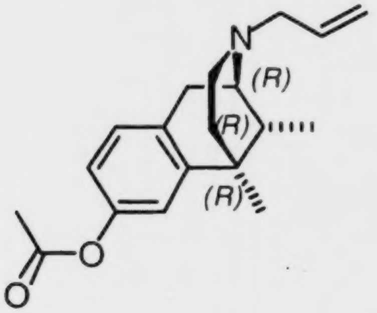
NIH 11044 (continued)

Comment: The results in the mouse indicate some weak analgesic and mu-opioid receptor antagonist properties. In the monkey, NIH 11044 appeared to be a mu-opioid receptor antagonist and kappa-opioid receptor agonist. A complete opioid subtype profiling in the mouse might be more revealing.

NIH 11045 (-)-(1*R*,5*R*,9*R*)-2'-Acetoxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan Oxalate



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

1) TF – 0% at 1 and 10, 5% at 30[a,b]
2) TF vs. M - 1.35 (0.76 - 2.39)
2) PPQ – 3% at 1, 8% at 10 and 13% at 30[a]
3) HP - Inactive at 1, 10 and 30[a]

[a]Increased locomotor activity at 30.
[b]Ataxia at 10 and 30.

Special Test: AD50 of NIH 11046 vs ED80 of enadoline, a selective kappa agonist, (0.3 mg/kg, s.c.) = 2.73 (1.43 - 5.22).

MONKEY DATA
(SDS)

With NIH 11045 there is evidence for heterogeneous opioid subtype activity in the morphine-dependent monkey in abrupt withdrawal. This compound displayed a behavioral profile not unlike that of NIH 11044. The signs designated jaw sag, ataxia, slowing, eyelid ptosis, tremors and salivation were noted. The effects appeared dose-related. The drug acted promptly and the duration of action was 90 to 120 min. In addition, 3 monkeys refused to leave their pen during the 30-min abdominal muscles check; 2 would not leave their pen during the 60-min examination; and, 1 would not leave its pen until the 120-min interval.

NIH 11045 (continued)

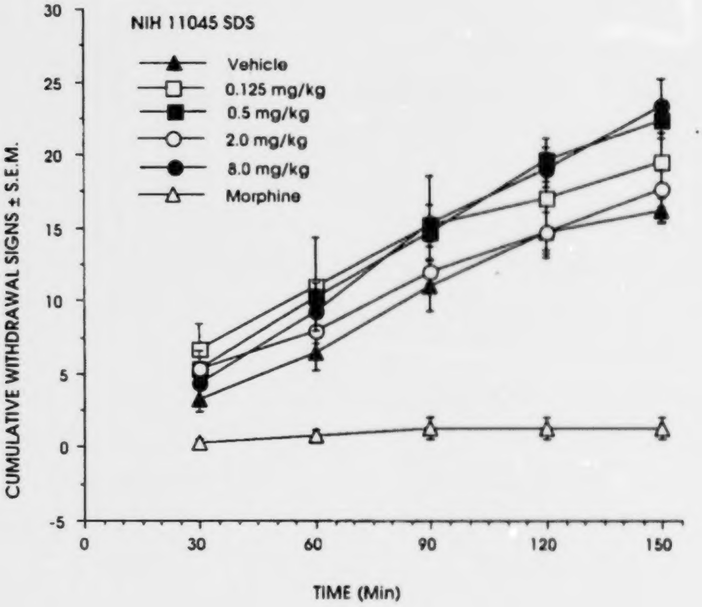
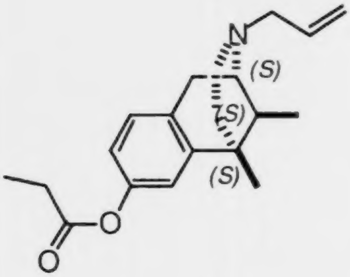


Fig NIH 11045 SDS. Results of study in which single doses of NIH 11045 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: In the mouse, NIH 11045 displayed mu- and kappa-opioid receptor antagonist activity. Its potency as a mu-opioid receptor antagonist was very weak or approximately 1/100 that of the reference standard, naloxone. Potency as a kappa-opioid receptor antagonist was about equivalent to that of norbinaltorphimine (nBNI). However, onset of action was much faster (30 min) than that of nBNI (2 hr). The behavioral profile in the withdrawn morphine-dependent monkey suggested mu- antagonist and kappa agonist properties.

NIH 11051 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-propenyl)-2'-propionoxy-6,7-benzomorphan Hydrochlorides



MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1 and 10, 10% at 30[a,d]
2) TF vs. M – Inactive at 1, 10 and 30[a,b,d]
3) PPQ – 3.57 (3.05 - 4.17)[a,d]
4) HP - Inactive at 1 and 10, 13% at 30[a,c,d]

[a] Ataxia, increased locomotor activity and Straub tail at 10 and 30.

[b] At 10 and 30, ataxia which was diminished in intensity after morphine.

[c] Slight ataxia at 6 mg/kg.

[d] Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

NIH 11051 (continued)

MONKEY DATA
(SDS)

NIH 11051 attenuated withdrawal signs (see figure). However, severe dose-related CNS depressant properties were noted. Slowing, ataxia and salivation were seen. One monkey fell from its perch but was fully recovered after 90 min.

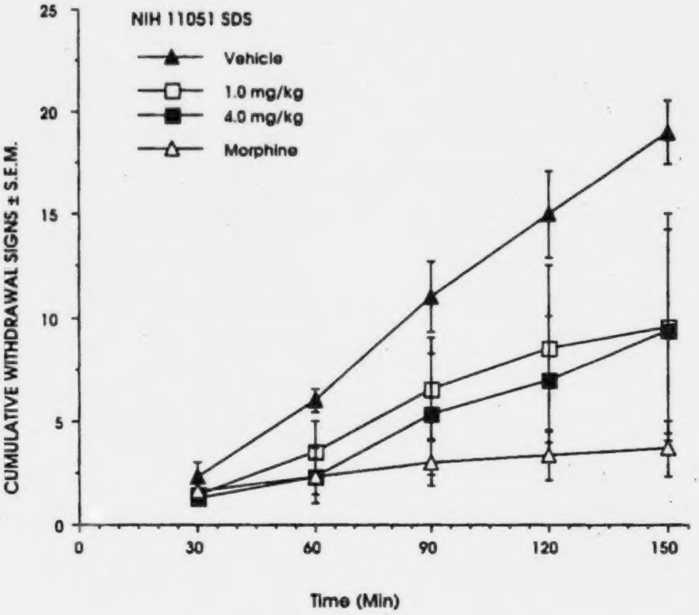
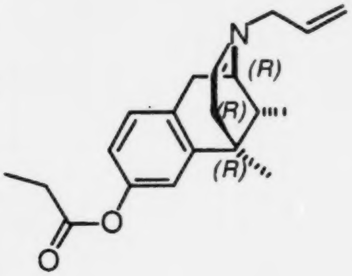


Fig NIH 11051 SDS. Results of study in which single doses of NIH 11051 were substituted for morphine in morphine-dependent monkeys in withdrawal.

Comment: The mice and monkeys showed behavioral signs consistent with those produced by CNS depressants. Limited supplies precluded a full evaluation.

NIH 11052 (-)-(1R,5R,9R)-5,9-Dimethyl-2-(2-propenyl)-2'-propionoxy-6,7-benzomorphan.HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1, 10 and 30a,b
2) TF vs. M – 0.30 (0.09 - 0.99)a,b
3) PPQ – 10.30 (3.76 - 28.27)a,b
4) HP - Inactive at 1, 10 and 30a,b

aAtaxia at 10 and 30.
bVehicle was 10% hydroxypropyl-□-cyclodextrin in water.

NIH 11052 (continued)

MONKEY DATA
(SDS)

As shown in the figure, NIH 11052 did not substitute for morphine, instead it exacerbated withdrawal at 1.0 mg/kg. Potency estimate is 1/20 that of naloxone, the reference standard.

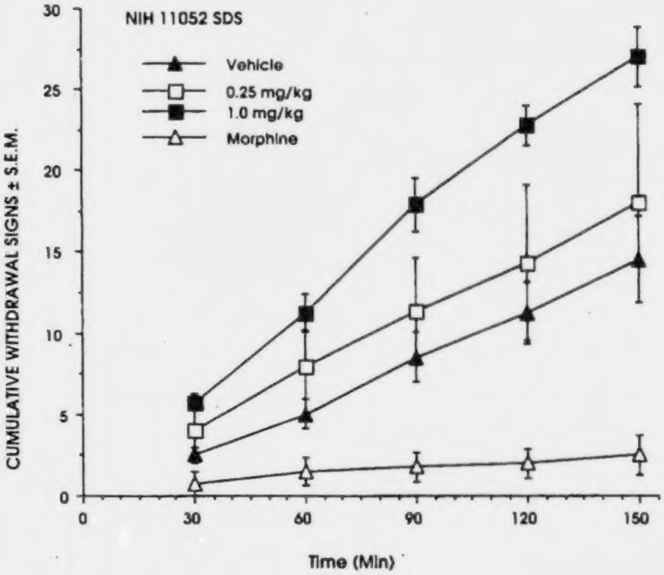
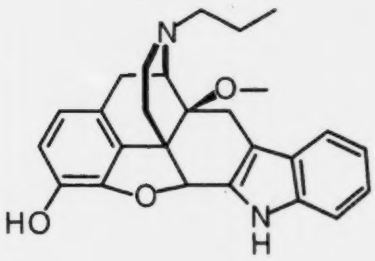


Fig. NIH 11052 SDS. Results of study in which single doses of NIH 11052 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: In the mouse, NIH 11052 displayed weak antinociceptive properties and low order opioid-receptor antagonism. In morphine-dependent rhesus monkeys, it demonstrated antagonist activity.

NIH 11063 4,5α-Epoxy-14β-methoxy-17-(propyl)indolo[2',3':6,7]morphinan-3-ol



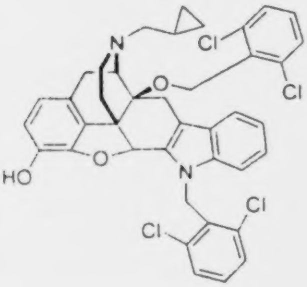
MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1 and 10.[a,b]
2) TF vs. M – 7% at 1, 4% at 10 and 0% at 30.[a,b]
3) PPQ – Inactive at 1.[a,b]
4) HP - 13% at 1.[a,b]

[a] Vehicle was 1% lactic acid in water.
[b] Drug supply exhausted.

Comment: In the dose range tested, NIH 11063 does not display remarkable opioid agonist or antagonist activity.

NIH 11069 1'-(2,6-Dichlorobenzyl)-14β-[(2,6-dichlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo[2',3':6,7]morphinan-3-ol·HCl



MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

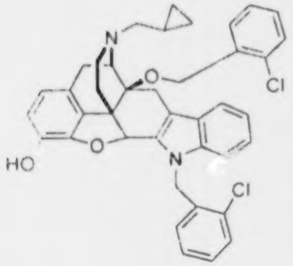
1) TF – 0% at 1, 11% at 3, 63% at 10 and 39% at 20.[a,b]
2) TF vs. M – 0% at 1, 11% at 3, 63% at 10 and 39% at 20.[a,b]
3) PPQ – Inactive at 3.[a,b]
4) HP - 13% at 1 and 37% at 10.[a,b]

[a] Drug was dissolved in 100% DMSO. When attempts were made to dilute this stock solution with water, particles formed and adhered to sides of container. Therefore, dilutions were made using 100% DMSO. Vehicle alone, 100% DMSO, produced 9% effect at 0.1 ml and 24% effect at 0.3 ml.

[b] Inactivity, eyelid ptosis, arched backs and large wheals at sites of injection.

Comment: This drug could not be reliably tested because of problems with solubility. Apparently DMSO, per se, accounts for the activity noted.

NIH 11070 1'-(3-Chlorobenzyl)-14β-[(3-chlorobenzyl)oxy]-17-cyclopropylmethyl-4,5α-epoxyindolo[2',3':6,7]-morphinan-3-ol.



MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

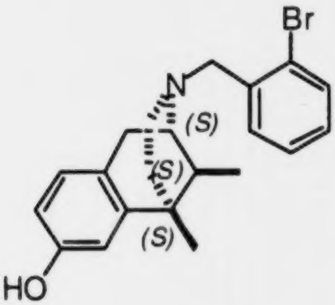
1) TF – 0% at 1, 63% at 10 and 11% 30.[a,b]
2) TF vs. M – Inactive at 1, 10 and 30.[a,b]
3) PPQ – 17% at 1, 0%10 and 34 % at 30.[a,b]
4) HP - 0% at 1, 25% at 10 and 37% at 30.[a,b]

[a] Drug was dissolved in 100% DMSO. When attempts were made to dilute this stock solution with water, particles formed and adhered to sides of container. Therefore dilutions were made using 100% DMSO. Vehicle alone, 100% DMSO, produced 11% effect at 0.1 ml and 12 to 86% effect at 0.3 ml.

[b] Inactivity, eyelid ptosis and large wheals at sites of injection.

Comment: This drug could not be reliably tested because of problems with solubility. Apparently DMSO per se, accounts for the activity noted.

NIH 11080 (+)-(1*S*,5*S*,9*S*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



NI

MOUSE DATA - ED50 OR AD50
(mg/kg or % change)

1) TF – Inactive at 1, 10 and 30[a]
2) TF vs. M - Inactive at 1, 4% at 10 and 21% at 30[a]
3) PPQ – Inactive at 1, 10 and 30[a]
4) HP - Inactive at 1, 13% at 10 and 30[a]

[a] Vehicle - 0.4% lactic acid in water.

MONKEY DATA
(SDS)

As shown in the figure, NIH 11080 did not substitute for morphine, Instead, it may have exacerbated withdrawal. Because of inadequate supplies, only 2 monkeys could be tested at the high dose (16.0 mg/kg).

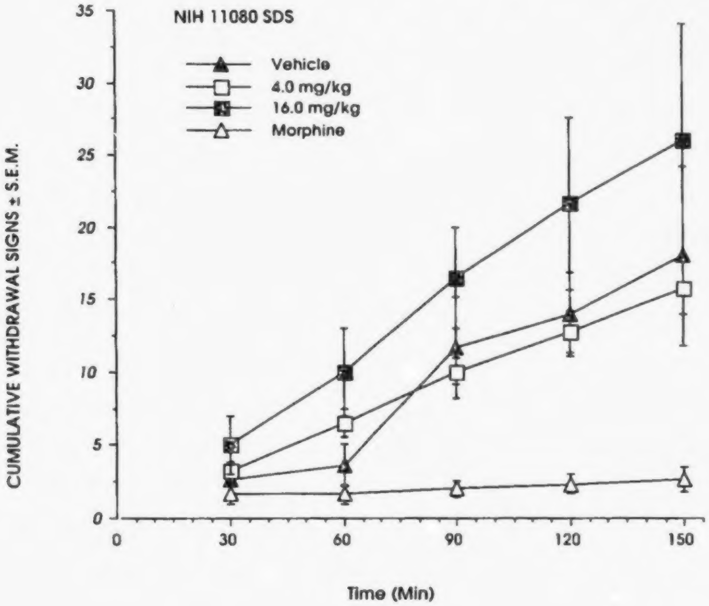
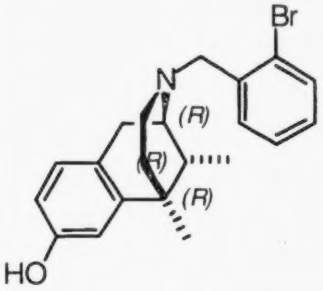


Fig NIH 11080 SDS. Results of study in which single doses of NIH 11080 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: The results in mice and monkeys suggest that NIH 11080 has weak mu-opioid antagonist properties. Drug supply was exhausted.

NIH 11081 (-)-(1*R*,5*R*,9*R*)-2-(2-Bromobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



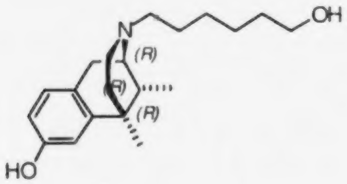
MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – 2% at 1, 4% at 10 and 8% at 30[a]
2) TF vs. M - 24% at 1, 35% at 10 and 24% at 30[a]
3) PPQ – 15% at 1 and inactive at 10 and 17% at 30[a]
4) HP - 13% at 1 and inactive at 10 and 13% at 30[a]

[a]Vehicle was 0.4% lactic acid in water.

Comment: As tested, NIH 11081 was devoid of opioid properties in mice.

NIH 11082 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan



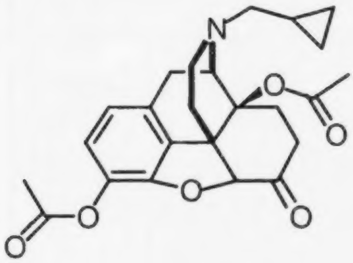
MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – Inactive at 1 and 10 and 20% at 30[a]
2) TF vs. M - Inactive at 1, 10 and 30[a]
3) PPQ – 1.93 (0.70 - 5.34)[a]
4) HP - Inactive at 1, 10, and 30[a]

[a] Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: Apparantly, NIH 11082 lacks mu-opioid properties in mice.

NIH 11083 3,14-Diacetoxynaltrexone Oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) (mg/kg or % change)

1) TF – 12% at 1 and inactive at 10 and 30[a]
2) TF vs. M - 0.0037 (0.0016 - 0.0086)[a]
3) PPQ – Inactive at 1 and 10, 3% at 30[a]
4) HP - Inactive at 1, 10 and 30[a]

[a] Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

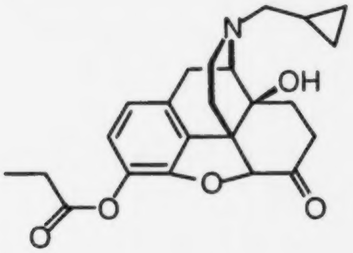
Time Course Study

NIH 11083, (AD80 = 0.03 mg/kg, s.c.,) Pretreatment:Time		
30 min	2 hr	24 hr
88% Antagonism	19% Antagonism	0% Antagonism

Morphine ED50 (5 mg/kg, s.c.) given 20 min before testing.

Comment: Although NIH 11083 is very potent mu-opioid receptor antagonist, its duration of action is not remarkable. Potency estimate is 10 times that of naloxone.

NIH 11084 3-Propionxylnaltrexone Oxalate



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

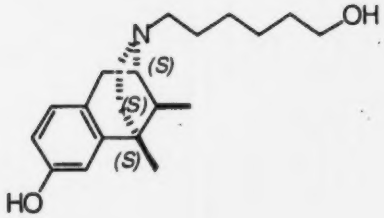
1) TF – Inactive at 1, 10 and 30*
2) TF vs. M - 0.01 (0.0034 - 0.034)*
3) PPQ – Inactive at 1 and 10, 3% at 30*
4) HP - Inactive at 1, 10 and 30*
*Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Time Course Study

NIH 11083, AD80 = 0.04 mg/kg, s.c.) Pretreatment Time		
30 min	2 hr	24 hr
93% Antagonism	24% Antagonism	Inactive

Comment: NIH 11084 is a potent mu-opioid receptor antagonist. However, its duration of action is short. Its potency is approximately equal to that of naloxone, the reference standard.

NIH 11085 (+)-(1*S*,5*S*,9*S*)-5,9-dimethyl-2'-hydroxy-2-(6-hydroxyhexyl)-6,7-benzomorphan Hydrochloride



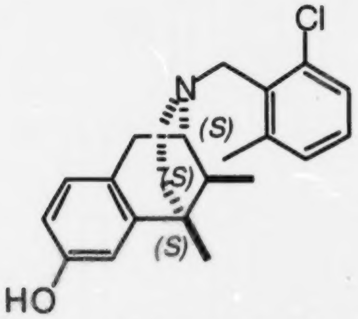
MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1 and 10, 9% at 30*
2) TF vs. M – Inactive at 1, 10 and 30*
3) PPQ –18% at 1, 8% at 3, 0% and 70% at 10 (tested twice at 10) and 40% and 16% at 30 (tested twice at 30)*
4) HP - 25% at 1, 13% at 10 and 0% at 30 ·
*Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: NIH 11085 displays a rather erratic dose-response in the PPQ test. This drug probably lacks mu-opioid receptor activity in mice.

*Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

NIH 11088 (+)-(1*S*,5*S*,9*S*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride

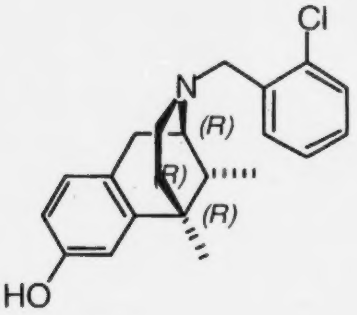


MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1, 10 and 30*
2) TF vs. M – 10% at 1, Inactive at 10 and 30*
3) PPQ – 18% at 1, 20% at 10 and Inactive at 30*
4) HP - 25% at 1, 13% at 3, Inactive at 10 and 30*
*Vehicle - 10% hydroxypropyl-β-cyclodextrin in water.

Comment: According to the results, NIH 11088 is inactive

NIH 11093 (-)-(1*R*,5*R*,9*R*)-2-(2-Chlorobenzyl)-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan Hydrochloride



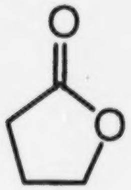
MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1, 10 and 30[a]
2) TF vs. M – Inactive at 1, 10 and 30[a]
3) PPQ – Inactive at 1, 16% at 10 and 14% at 30[a]
4) HP - 25% at 1, 13% at 10 and 30% at 30[a]

[a] Vehicle was 10% hydroxypropyl-β-cyclodextrin in water.

Comment: Antinociceptively speaking, the drug is essentially inactive.

NIH 11094 gamma-Butyrolactone, Also, NIH 10540

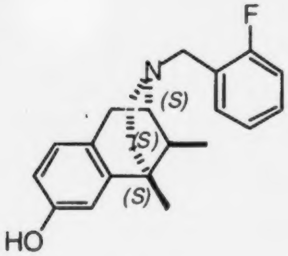


MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1, 10 and 30
2) TF vs. M – Inactive at 1, 13% at 10 and inactive at 30
3) PPQ – Inactive at 1, 3% at 10 and 53% at 30
4) HP - 25 % at 1, Inactive at 10 and 30

Comment: NIH 11094 appears to be devoid of opioid activity. Studies in mice and morphine-dependent monkeys were reported previously (NIDA Monograph 81, 1988, pp541-542). This drug was reported to be inactive in the TF test and active in the PPQ test. It neither substituted for morphine nor exacerbated withdrawal in morphine-dependent rhesus monkeys.

NIH 11095 (+)-(1*S*,5*S*,9*S*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7-benzomorphan Oxalate



MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1, 10 and 30
2) TF vs. M – Inactive at 1, 10 and 30
3) PPQ – 14% at 1, Inactive at 10 and 39% at 30
4) HP - Inactive at 1 and 30, 13% at 10

Comment: As tested, NIH 11095 is unremarkable, antinociceptively

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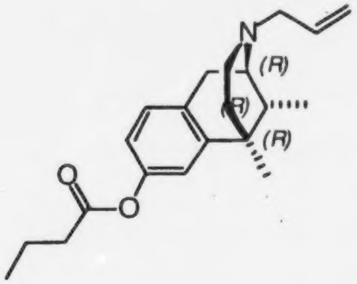
NIH 11096 (-)-(1*R*,5*R*,9*R*)-2'-Butyroxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan Hydrochloride



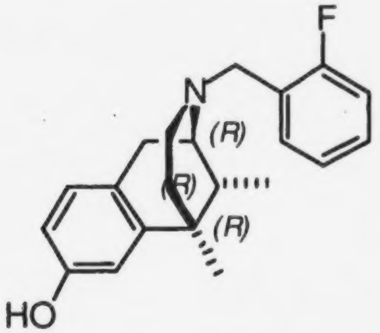
MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1, 10 and 30[a,c]
2) TF vs. M – 0.29 (0.09 - 0.93)[c]
3) PPQ – Inactive at 1 and 10, 27% at 30[a,c]
4) HP - 13% at 1, Inactive at 10 and 13% at 30[a,b,c]

[a] At 30 mg/kg, mild ataxia.
[b] At 30 mg/kg, hyperactivity.
[c] Vehicle was 20% hydroxyppropyl-β-cyclodextrin in water.

Comment: Apparently, NIH 11096 has mu-opioid antagonist effects. Potency estimate is approximately 1/10 that of naloxone, the reference standard.

NIH 11097 (-)-(1*R*,5*R*,9*R*)-5,9-Dimethyl-2-(2-fluorobenzyl)-2'-hydroxy-6,7- benzomorphan Oxalate



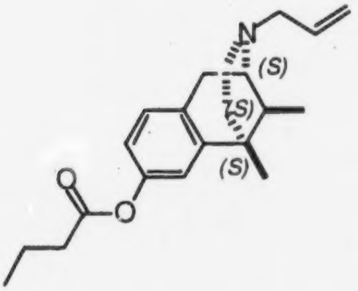
MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1, 9% at 10 and 13% at 30[a]
2) TF vs. M – Inactive at 1 and 30, 18% at 10[a]
3) PPQ – 7% at 1, 10% at 10 and 27% at 30[a]
4) HP - 13% at 1 and 10, Inactive at 30[a]

[a] Vehicle was 20% hydroxypropyl-β-cyclodextrin in water.

Comment: As tested, this compound is not remarkable as an opioid.

NIH 11098 (+)-(1*S*,5*S*,9*S*)-2'-Butyroxy-5,9-dimethyl-2-(2-propenyl)-6,7-benzomorphan Hydrochloride



MOUSE DATA - ED50 OR AD50
(95 % C.L.) mg/kg or % change

1) TF – Inactive at 1, 10 and 30[a,d]
2) TF vs. M – Inactive at 1, 10 and 30[a,b,d]
3) PPQ – 9.6 (4.4 - 21.0)[a,c,d]
4) HP - Inactive at 1, 13% at 10 and inactive at 30[a,c,d]

[a] At 30 mg/kg, ataxia and mild Straub tail.
[b] At 20 mg/kg, ataxia prior to morphine, Straub tail.
[c] Ataxia at 3, 10 and 30, increased respiration at 30.
[d] Vehicle was 20% hydroxypropyl-β-cyclodextrin in water.

Comment: This drug does not display activity reminiscent of mu-opioid receptor agonists or antagonists.

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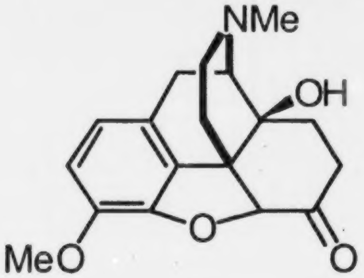
NIH 11107 Oxycodone Hydrochloride



MOUSE DATA - ED50 OR AD50
% C.L.) (mg/kg or % change)

1) TF – 0.94 (0.4 - 2.2)[a]
2) TF vs. M - Inactive at 1, 10 and 30 [a,b]
3) PPQ – 0.38 (0.19 - 0.75)
4) HP - 1.37 (0.48 - 3.92)[a]

[a] Straub tail and increased locomotor activity.

[b] Onset within 5 min prior to morphine. Paws were arched.

Special Tests:

1) Opioid subtype testing
   a) Naltrindole (s.c.) vs ED80 of NIH 11107 in TF: 0% at 1 and 10, 15% at 30.
   b) Nor-BNI (s.c., 120 min pretreatment time) vs ED80 of NIH 11107 (s.c.,) in TF: Inactive at 1, 10 and 30).
   c) β-FNA (i.c.v., 240 min pretreatment time) vs ED80 of NIH 11107 (s.c.) in TF: AD50 = 1.23 (0.27 - 5.56) μg/brain.

MONKEY DATA
(SDS)

NIH 11107 substituted completely for morphine in morphine-dependent monkeys in withdrawal. Onset and offset of actions were equivalent to those of morphine.

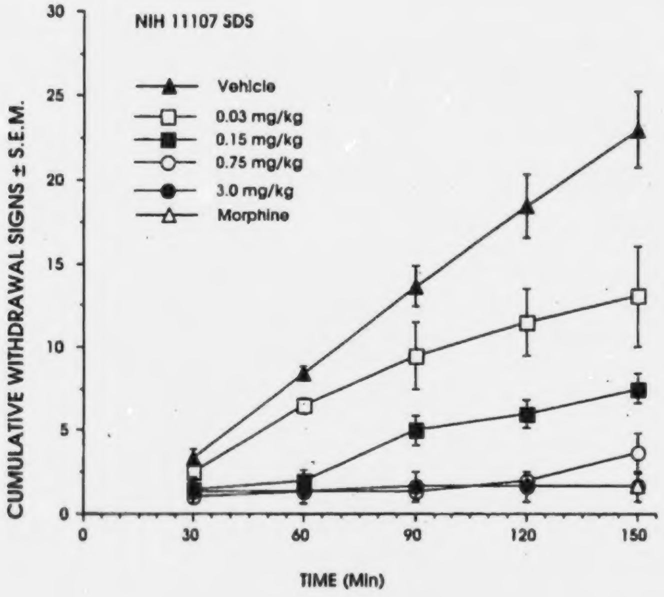


Fig NIH 11107 SDS. Results of study in which single doses of NIH 11107 were substituted for morphine in morphine-dependent monkeys in withdrawal

Comment: Oxycodone was classified as an opioid in 1957. The growing incidence of OxyContin abuse by humans prompted us to scrutinize in more detail its opioid properties. Oxycodone hydrochloride was found to be more active than morphine sulfate, antinociceptively speaking, in mice. It was without activity, as an antagonist, versus morphine. In addition, beta-funaltrexamine antagonized the ED80 of oxycodone indicating it was a potent mu-opioid receptor agonist. We did not find evidence that oxycodone had kappa-opioid agonist properties as reported by (Ross and Smith, 1997). In our hands, nor-BNI, a kappa antagonist, was inactive up to 30 mg/kg. In vivo studies by Spetea and coworkers (1998), indicated high affinity binding at delta-opioid sites and lesser potency for mu- and kappa-opioid sites. In our evaluation, naltrindole, a delta opioid antagonist, was inactive up to 30 mg/kg. In morphine-dependent rhesus monkeys in withdrawal, oxycodone dose-dependently substituted completely for morphine. Onset and duration of actions were equivalent to those of morphine; however, oxycodone was approximately 2 to 3 times more potent than morphine. We conclude that oxycodone is a selective mu-opioid receptor agonist.

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PROGRESS REPORT FROM THE TESTING PROGRAM FOR STIMULANT AND DEPRESSANT DRUGS (2002)

L.R. McMahon, C.P. France, G. Winger and W.L. Woolverton

The University of Texas Health Science Center at San Antonio, TX; University of Michigan, Ann Arbor, MI; University of Mississippi Medical Center, Jackson, MS

INTRODUCTION

The research group involved in the evaluation of stimulant and depressant compounds has been in existence for approximately 18 years. The group now includes laboratories at The University of Texas Health Science Center at San Antonio (UTHSCSA; France, McMahon), University of Michigan (UM; Winger) and University of Mississippi Medical Center (UMMC; Woolverton), and is part of the Drug Evaluation Committee (J. Woods, Chair) of the College on Problems of Drug Dependence (CPDD) which is supported by both the CPDD and the National Institute on Drug Abuse (NIDA). One of the purposes of the group is to evaluate new compounds, generally classified as either stimulants or depressants, for their abuse liability and physical dependence potential. Compounds are received, coded and distributed by A. Coop at the University of Maryland School of Pharmacy (Baltimore) for blind testing in the various laboratories. They are evaluated for reinforcing effects in monkeys that previously self-administered methohexital (UM), and for discriminative stimulus effects in pentobarbital-trained monkeys (UMMC), midazolam-trained monkeys (UTHSCSA), and flumazenil-trained monkeys that receive diazepam daily (UTHSCSA). This report includes the results of evaluation of CPDD 0060, CPDD 0061 and CPDD 0062. All studies were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee, UTHSCSA, UM, UMMC, and the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

METHODS

Reinforcing Effects in Rhesus Monkeys (UM)

Subjects

Subjects were rhesus monkeys (*Macaca mulatta*) experienced with self-administration of sodium methohexital. Animals were surgically prepared with indwelling silicone rubber catheters using 10 mg/kg i.m. ketamine and 2.0 mg/kg i.m. xylazine as anesthetics. Catheters were implanted in jugular (internal or external), femoral or brachial veins as necessary. Catheters passed subcutaneously (s.c.) to the mid-scapular region, exited the body and continued, through a hollow restraining arm, to the outside rear of the cage.

Apparatus

The restraint and catheter protection devices are described in detail by Deneau *et al.* (1969). Each monkey wore a tubular stainless steel harness that protected the exit site of the catheter and allowed relatively unrestricted movement within the cage. A Teflon cloth jacket (Alice King Chatham Medical Arts, Los Angeles, CA) provided further protection of the catheter for some animals. The harness was connected to a flexible spring arm that carried the catheter to the back of the cage where it joined tubing passing through a roller infusion pump (Watson and Marlow Co., Model MHRK 55, Falmouth, UK).

Monkeys were individually housed in stainless steel cages, measuring 83.3 X 76.2 X 91.4 cm deep. A 15.4 cm square stimulus panel was located on the side of each cage, approximately 10 cm from the front and 19 cm from the bottom of the cage. Across the top of the stimulus panel, 1.5 cm apart, were three circular, 2.5 cm in diameter, translucent plastic stimulus lights that could be illuminated by 5 W colored bulbs. The two side lights could be illuminated red and the center light green. Below each of the two red stimulus lights was a response lever (Model 121-07; BRS-LVE, Beltsville, MD) capable of being operated by a force of 0.010 to 0.015 N. Experimental control was provided by an IBM PS/2 computer programmed with Med-PC (Med-Associates, Fairfield, VT) software and located in an adjoining room.

Procedure

Reinforcing effects of CPDD 0060, CPDD 0061 and CPDD 0062 were evaluated in a substitution self-administration procedure in monkeys who were experienced with i.v. self administration of methohexital. Test sessions and baseline sessions had the same general structure. At the start of each session, a red light was illuminated over one of two levers. When a monkey completed the fixed-ratio requirement of 10 presses on that lever (fixed-ratio [FR] 10), a 5-second, 1.0 ml injection of saline, sodium methohexital (0.1 mg/kg), or a test compound was delivered. The red light was extinguished and a center green light was illuminated for the duration of the infusion. Each injection was followed by a 10-second timeout during which all stimulus lights were extinguished and responding had no programmed consequence.

Twice daily experimental sessions lasted 130 minutes each. On approximately half of the baseline sessions, the monkeys could respond for saline. All animals showed clear and consistent differential responses to saline and methohexital before test compounds were evaluated. In test sessions a dose of the test compound was made available for one session. Other conditions were similar to those of the baseline sessions.

Drugs

Four doses (0.1, 0.3, 1.0, and 3.2 mg/kg/injection) of CPDD 0060 and CPDD 0061 were studied in four and three monkeys, respectively. Three doses (0.1, 0.3 and 1.0 mg/kg/injection) of CPDD 0062 were studied in three monkeys and a larger dose (3.2 mg/kg/injection) was studied in one of the three monkeys. Doses of CPDD 0060, CPDD 0061 or CPDD 0062 larger than 3.2 mg/kg/injection could not be studied due to limitations in solubility. CPDD 0060 and CPDD 0061 were dissolved in saline and CPDD 0062 and methohexital sodium were dissolved in sterile water.

Discriminative Stimulus Effects in Rhesus Monkeys (pentobarbital discrimination, UMMC)

Subjects

Four adult rhesus monkeys were housed individually in stainless steel cages; water was available continuously. They received 120 to 200 g of Teklad monkey chow after each session and a chewable vitamin tablet 3 times per week.

The monkeys had been trained previously to discriminate pentobarbital from saline in a two-lever, discrete-trial shock avoidance procedure. All monkeys had received other test drugs prior to CPDD 0060, CPDD 0061 and CPDD 0062.

Apparatus

During experimental sessions animals were seated in primate restraint chairs and placed inside sound-attenuating cubicles. All chairs were fitted with shoes containing brass plates in the soles that permitted delivery of electric shock produced by a shock generator (SG 903 BRS/LVE, Laurel, MD). Chambers were equipped with two response levers (PRL-001, BRS/LVE, Laurel, MD) mounted on one wall. There were four white lights above each lever. Chambers were illuminated with ceiling-mounted 40w incandescent house lights. Experimental events were programmed and recorded with an Apple Macintosh II computer that was located in a room adjacent to the one in which animals were tested.

Procedure

The training and test procedures have been reported in detail elsewhere (Woolverton *et al.*, 1994). A monkey was placed in the restraint chair and either saline (1-2 ml) or the training drug was administered intragastrically (i.g.) via a nasogastric tube, followed by a 1.5 ml saline flush. Fifty-five minutes after infusion, the monkey was placed into the experimental chamber.

The session began with a 5-minute timeout that was followed by 30 trials. On each trial the house light and lever lights were illuminated and responding on the correct lever postponed scheduled shock and extinguished the lights. Incorrect responses reset the response requirement on the correct lever. The correct lever was determined by the pre-session infusion (drug or saline). If the response requirement (FR 5) was not satisfied on the correct lever within

10 seconds of the onset of the lights, shock (250-msec, 5-mA) was delivered. If the response requirement was not satisfied within 4 additional seconds, a second shock was delivered and the trial ended. The session was terminated when 2 shocks were delivered in 2 consecutive trials or after 30 trials. Consecutive trials were separated by 30-sec timeouts.

Training sessions were conducted five days a week according to the following schedule: SDDSS, DSSDD, where S denotes sessions preceded by saline and D denotes sessions preceded by drug. Discrimination training continued until at least 90% of the responses in the first trial were on the correct lever and subjects avoided shock on at least 90% of the trials (27/30) for seven out of eight consecutive sessions. When subjects failed to satisfy criteria, the training sequence was continued until the criteria were satisfied. Test sessions were identical to training sessions except that test drugs were administered and completing the response requirement on either lever postponed scheduled shock.

Drugs

Pentobarbital was mixed daily by diluting Nembutal (Abbott Laboratories, North Chicago, IL) with saline. The training dose of pentobarbital was 5.6 (8814-Ru) or 10 mg/kg i.g. Four doses (30, 100, 300 and 560 mg/kg) of CPDD 0060, four doses (10, 30, 100 and 300 mg/kg) of CPDD 0061, and four doses (1, 3, 10 and 30 mg/kg) of CPDD 0062 were studied. CPDD 0060 and CPDD 0061 were dissolved in water and the infusion volumes were 0.25-0.5 ml/kg. CPDD 0062 was prepared in a 40 mg/ml stock solution that was 1:1 Alkamuls EL620:95% ethanol. For lower doses of CPDD 0062, saline was added to an appropriate amount of stock solution to allow an infusion volume of 0.25 ml/kg. For 30 mg/kg of CPDD 0062, the infusion volume was 0.85 ml/kg.

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations, UTHSCSA)

Subjects

Six rhesus monkeys, weighing between 3.5 and 10.0 kg, were housed individually in stainless steel cages. Water was continuously available and monkeys received primate chow (Harlan Teklad, Madison, WI) daily as well as fresh fruit and peanuts several days per week.

Apparatus

Monkeys were seated in chairs that provided restraint at the neck. For midazolam discriminating monkeys, chairs were equipped with shoes containing brass electrodes, to which brief (250 msec) electric shock could be delivered from a.c. generators located adjacent to the chambers. During experimental sessions, chairs were located in sound-attenuating, ventilated chambers that were equipped with several response levers, a food cup and an array of stimulus lights.

Procedure

Flumazenil Discrimination. Monkeys consumed 5.6 mg/kg of diazepam in 45-50 ml of fruit punch 3 hrs prior to daily sessions in which they discriminated between s.c. injections of 0.1 (JI) or 0.32 mg/kg of flumazenil and vehicle while responding under a FR 5 schedule of food presentation (Gerak and France, 1999). Daily training sessions consisted of several discrete, 15-minute cycles. Each cycle comprised a 10-minute timeout, during which the chamber was dark and lever presses had no programmed consequence, followed by a response period, during which the chamber was illuminated green and monkeys could receive food by responding five times on the appropriate lever as determined by the s.c. injection administered during the first minute of the 10-minute timeout (e.g., left lever after vehicle, right lever after flumazenil). The response period ended after 5 minutes or the delivery of 10 food pellets, whichever occurred first. Responses on the injection-inappropriate lever reset the response requirement on the correct lever.

Test sessions were conducted following training sessions in which ≥80% of the total responses occurred on the lever designated correct by the injection administered during the first min of the cycle and fewer than five responses occurred on the incorrect lever prior to completion of the FR response requirement on the correct lever. Prior to each test, these criteria had to be satisfied for training sessions during which flumazenil and vehicle injections were administered. The type of training session preceding test sessions varied non-systematically. Test sessions were

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identical to training sessions except that various doses of flumazenil were administered during the first minute of each timeout (cumulative dosing procedure); otherwise, various doses of a test compound were administered prior to or during the first minute of the first cycle followed by vehicle or sham injections during the first minute of subsequent cycles (time course procedure). Five consecutive responses on either lever resulted in food delivery. Substitution for flumazenil was defined as ≥80% responding on the drug-appropriate lever.

Midazolam Discrimination. Monkeys discriminated between s.c. injections of 0.32 mg/kg of midazolam and vehicle while responding under a FR 10 schedule of stimulus-shock termination (Lelas *et al.*, 1999). Daily sessions comprised multiple, 15-minute cycles each comprising a 10-minute timeout, during which the chamber was dark and lever presses had no programmed consequence, followed by a response period, during which the chamber was illuminated red and shocks were scheduled to occur every 15 sec. Monkeys could prevent scheduled shocks for 30 seconds by completing the response requirement.

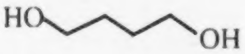
Test sessions were conducted following training sessions in which ≥80% of the total responses occurred on the lever designated correct by the injection administered during the first min of the cycle and fewer than ten responses occurred on the incorrect lever prior to completion of the FR response requirement on the correct lever. Prior to each test, these criteria had to be satisfied for training sessions during which midazolam and saline injections were administered. The type of training session preceding test sessions varied non-systematically. Test sessions were identical to training sessions except that various doses of midazolam were administered during the first minute of each timeout (cumulative dosing procedure); otherwise, various doses of a test compound were administered prior to or during the first minute of the first cycle followed by saline or sham injections during the first minute of subsequent cycles (time course procedure). Ten consecutive responses on either lever postponed the shock schedule. Substitution for midazolam was defined as ≥80% responding on the drug-appropriate lever.

Drugs

Diazepam (Zenith Laboratories, Northvale, NJ) was suspended in 45-50 ml (depending on body weight) of fruit punch containing suspending Agent K to yield a dose of 5.6 mg/kg/daily drinking episode. Flumazenil (F. Hoffman LaRoche, LTD, Basel, Switzerland) was dissolved in a vehicle of 10% ethanol, 40% propylene glycol and 50% saline; midazolam hydrochloride was prepared commercially (Roche Pharma, Inc., Manati PR). CPDD 0060 (32, 100 and 320 mg/kg in flumazenil discriminating monkeys; 100, 320 and 560 mg/kg in midazolam discriminating monkeys) was administered s.c. 2 hrs prior to 2-hr sessions. CPDD 0061 (100, 178 and 320 in flumazenil and midazolam discriminating monkeys; 560 mg/kg also in midazolam discriminating monkeys) was administered s.c. at the beginning of 2-hr sessions. CPDD 0062 (32 and 100 mg/kg) was administered s.c. at the beginning of 2-hr sessions in flumazenil and midazolam discriminating monkeys. CPDD 0060 and CPDD 0061 were dissolved in saline and CPDD 0062 was dissolved in 50% ethanol and 50% emulphor.

RESULTS

CPDD 0060
1,4-Butanediol (1,4-BDL)

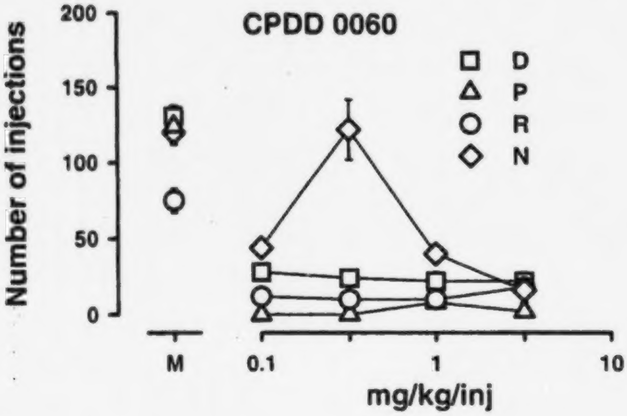


Reinforcing Effects in Rhesus Monkeys

Figure 1 shows the results of self-administration studies with CPDD 0060 in four monkeys experienced with self-administration of methohexital. Each symbol designates the number of injections taken by the individual monkeys. The symbols over M represent the number of injections of sodium methohexital averaged over two sessions that occurred prior to evaluation of the first, smallest dose of CPDD 0060. Data for sessions in which saline was delivered contingent on responding are not shown and were typically 10-15 injections per session.

In three of the four monkeys, CPDD 0060 maintained low levels of responding across all tested doses; no reinforcing effect was shown by this drug at these doses. In monkey N, at a single dose of 0.32 mg/kg/injection, CPDD 0060 maintained behavior that was greater than that maintained by saline. N is a monkey that often shows reinforcing effects of drugs that other monkeys do not report as reinforcing. His behavior is therefore interesting, but somewhat atypical. Results with monkey N might indicate that CPDD 0060 has reinforcing effects in some individuals.

Figure 1 Self-administration of CPDD 0060 in monkeys experienced with methohexital



Discriminative Stimulus Effects in Rhesus Monkeys (pentobarbital discrimination)

Monkeys that discriminated between saline and pentobarbital responded ≥95% on the injection-appropriate lever during test sessions with the training drug or vehicle (Table 1). When administered 60 minutes before the session, CPDD 0060 engendered little or no drug-appropriate responding (Table 1). Response rates were not systematically affected, except for a small decrease in monkey 8814 at the largest doses. When pretreatment time was varied between 120 and 240 minutes for doses of 100 and 300 mg/kg, no drug-appropriate responding was observed, and 100 mg/kg had no effect on response rates (Table 2). However, 300 mg/kg of CPDD 0060 decreased response rate when administered 120 minutes before the session, an effect that was diminished when the compound was administered 180 minutes before the session. After sessions in which response rate was decreased, monkeys were sedated and ataxic. These results demonstrate that CPDD 0060 did not have pentobarbital-like discriminative stimulus effects in rhesus monkeys when administered i.g. in doses up to 560 mg/kg, even under conditions in which response rate was decreased and sedative-like effects were observed.

Table 1 Discriminative stimulus effects of i.g. administration of CPDD 0060 in monkeys discriminating pentobarbital: dose response

			CPDD 0060 Dose (mg/kg)			
Subject	Pentobarbital	Saline	30	100	300	560
Ef3-E	100 / 2.2	3 / 2.5	0 / 3.6	0 / 3.3	0 / 2.2	nt
AQ63-G	100 / 2.2	0 / 3.0	0 / 3.0	0 / 2.8	0 / 2.5	0 / 2.8
17015-Ro	96 / 2.1	5 / 2.4	nt	0 / 3.1	0 / 2.7	nt
8814-Ru	100 / 1.3	0 / 2.0	0 / 1.9	0 / 1.9	18 / 1.0	10 / 1.1

Monkeys were trained to discriminate 5.6 (8814) or 10.0 mg/kg pentobarbital (i.g.) from saline in a discrete trial shock-avoidance termination paradigm. The response requirement was FR 5. Data represent the percent drug-appropriate trials / average response rate (responses / second). CPDD 0060 was administered via nasogastric tube 60 minutes prior to testing. In all cases 30 trials were completed. Doses of CPDD 0060 up to 300 mg/kg were tested twice, except in monkey 17015 where they were tested once; 560 mg/kg was tested once. nt=not tested.

Table 2 Discriminative stimulus effects of i.g. administration of CPDD 0060 in monkeys discriminating pentobarbital: time course

	CPDD 0060 (100 mg/kg)			CPDD 0060 (300 mg/kg)	
	Time (min)			Time (min)	
Subject	120	180	240	120	180
Ef3-E	0 / 3.0	0 / 2.5	0 / 2.7	* / 0.1	0 / 0.4
AQ63-G	0 / 3.1	0 / 2.8	0 /3.0	0 / 1.5	0 / 2.7
17015-Ro	0 / 2.8	nt	nt	0 / 2.6	0 / 2.7
8814-Ru	0 / 2.1	0 / 2.1	0 / 1.8	28 / 0.2	0 / 0.2

CPDD 0060 was administered via nasogastric tube at various time points (120-240 min) prior to testing. Doses of CPDD 0060 were tested once. *No completed trials. nt=not tested. See Table 1 for other details.

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations)

In monkeys receiving diazepam daily and discriminating between flumazenil and vehicle, flumazenil produced dose-related increases in the percentage of responses on the drug-associated lever with a dose of 0.1 mg/kg occasioning ≥80% drug-lever responding (Table 3). Administration of CPDD 0060 (32, 100 and 320 mg/kg) 2 hrs prior to 2-hr sessions did not substitute (i.e. produce ≥80% DR) for the flumazenil discriminative stimulus in any monkey (Table 4). A dose of 32 mg/kg of CPDD 0060 did not alter response rate. A dose of 100 mg/kg of CPDD 0060 substantially decreased response rate in one monkey (JI) and a dose of 320 mg/kg of CPDD 0060 suppressed responding in two monkeys (DA and ROL).

Table 3 Discriminative stimulus effects of flumazenil in diazepam (5.6 mg/kg/day) treated rhesus monkeys discriminating flumazenil: dose response

Subject	Flumazenil Dose (mg/kg) Veh	0.01	0.032	0.1
DA	2 / 0.76	11 / 2.33	33 / 1.48	90 / 2.06
ROL	0 / 1.39	4 / 1.43	10 / 1.71	86 / 1.50
JI	0 / 1.45	0 / 1.75	18 / 1.79	85 / 1.26

Monkeys were trained to discriminate 0.1 mg/kg (JI) or 0.32 mg/kg (s.c.) flumazenil from vehicle under a schedule of food presentation. The response requirement was FR 5. Data represent the percent drug-appropriate responding / response rate (responses / second).

Table 4 Discriminative stimulus effects of CPDD 0060 in diazepam (5.6 mg/kg/day) treated rhesus monkeys discriminating flumazenil: dose response

Subject	CPDD 0060 Dose (mg/kg) 32	100	320
DA	12 / 1.32	2 / 1.19	* / 0
ROL	1 / 1.25	4 / 1.41	* / 0
JI	4 / 1.51	* / 0.29	nt

CPDD 0060 was administered s.c. 2 hrs before sessions and data are the average of 8 cycles in a 2-hr session. *Discrimination data are not presented when response rate was <20% of control response rate. nt = not tested. See Table 3 for other details.

In monkeys discriminating between midazolam and saline, midazolam produced dose-related increases in the percentage of responses on the drug-associated lever with a dose of 0.1 (LI) or 0.32 mg/kg occasioning ≥80% drug-lever responding (Table 5). Administration of CPDD 0060 (100, 320 and 560 mg/kg) 2 hrs prior to 2-hr sessions did not substitute (i.e. produce ≥80% DR) for the midazolam discriminative stimulus in any monkey (Table 6). A dose of 100 mg/kg of CPDD 0060 did not alter response rate. A dose of 320 mg/kg of CPDD 0060 suppressed responding in one monkey (RO) and a dose of 560 mg/kg of CPDD 0060 substantially decreased responding in another monkey (SA).

Table 5 Discriminative stimulus effects of midazolam in rhesus monkeys discriminating midazolam: dose response

	Midazolam Dose (mg/kg)				
Subject	Veh	0.01	0.032	0.1	0.32
RO	0 / 2.61	0 / 2.41	0 / 2.43	21 / 2.72	100 / 1.90
LI	0 / 2.23	0 / 1.95	0 / 1.74	100 / 1.35	nt
SA	0 / 2.36	nt	0 / 2.46	36 / 1.40	93 / 1.00

Monkeys were trained to discriminate 0.32 mg/kg (s.c.) midazolam from saline under a schedule of stimulus-shock termination. The response requirement was FR 10. Data represent the percent drug-appropriate responding / response rate (responses / second). nt=not tested.

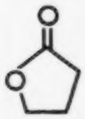
Table 6 Discriminative stimulus effects of CPDD 0060 in rhesus monkeys discriminating midazolam: dose response

	CPDD 0060 (mg/kg)		
Subject	100	320	560
RO	0 / 2.49	* / 0	nt
LI	0 / 2.28	0 / 1.26	nt
SA	0 / 2.50	0 / 1.40	* / 0.4

CPDD 0060 was administered s.c. 2 hrs before sessions and data are the average of 8 cycles in a 2-hr session. *Discrimination data are not presented when response rate was <20% of control response rate. nt = not tested. See Table 5 for other details.

CPDD 0061

Gamma-butyrolactone (GBL)



Reinforcing Effects in Rhesus Monkeys

Figure 2 shows results of self-administration studies with CPDD 0061 in three monkeys experienced with self-administration of methohexital. Each symbol designates the number of injections taken by the individual monkeys. The symbols over M represent the number of injections of sodium methohexital averaged over two sessions that occurred prior to evaluation of the first, smallest dose of CPDD 0061. Data for sessions in which saline was delivered contingent on responding are not shown and were typically 10-15 injections per session.

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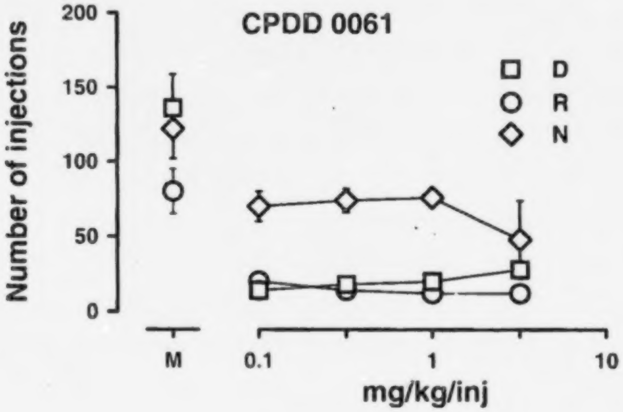
In each of the three monkeys, CPDD 0061 maintained low levels of responding across all tested doses; no reinforcing effect was shown by this drug at these doses. Monkey N showed generally higher intake than the other two monkeys, and he showed consistent responding across all doses.

Figure 2 Self-administration of CPDD 0061 in monkeys experienced with methohexital



Discriminative Stimulus Effects in Rhesus Monkeys (pentobarbital discrimination)

When administered 60 minutes before the session, CPDD 0061 engendered no drug-appropriate responding in the pentobarbital-trained monkeys (Table 7) up to a dose (300 mg/kg) that eliminated responding. When pretreatment time was increased to 120 or 180 minutes for doses of 100 and 300 mg/kg, no drug-appropriate responding was observed, and 100 mg/kg had no effect on response rates (Table 8). However, 300 mg/kg of CPDD 0061 eliminated responding when administered 120 minutes before the session. After sessions in which response rate was decreased, monkeys were sedated and ataxic. These results demonstrate that CPDD 0061 did not have pentobarbital-like discriminative stimulus effects in rhesus monkeys when administered i.g. in doses up to 300 mg/kg, even under conditions in which response rate was decreased and sedative-like effects were observed.

Table 7 Discriminative stimulus effects of i.g. administration of CPDD 0061 in monkeys discriminating pentobarbital: dose response

Subject	Pentobarbital	Saline	CPDD 0061 (mg/kg) 10	30	100	300
Ef3-E	100 / 2.2	3 / 2.5	0 / 3.1	0 / 3.1	0 / 2.6	* / 0.2
AQ63-G	100 / 2.2	0 / 3.0	0 / 2.9	0 / 3.1	0 / 2.9	* / 0.1
17015-Ro	96 / 2.1	5 / 2.4	nt	nt	0 /2.8	0 / 2.5
8814-Ru	100 / 1.3	0 / 2.0	0 / 2.3	0 / 2.3	0 / 1.8	* / 0

CPDD 0061 was administered via nasogastric tube 60 minutes prior to testing. Doses of CPDD 0061 were tested twice, except in monkey 17015 where 100 mg/kg was tested once. *No completed trials. nt=not tested. See Table 1 for other details.

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Table 8 Discriminative stimulus effects of i.g. administration of CPDD 0061 in monkeys discriminating pentobarbital: time course

Subject	CPDD 0061 (100 mg/kg) Time (min) 120	CPDD 0061 (100 mg/kg) Time (min) 180	CPDD 0061 (300 mg/kg) Time (min) 120	CPDD 0061 (300 mg/kg) Time (min) 180
Ef3-E	0 / 2.8	0 / 2.3	* / 0	* / 0
AQ63-G	0 / 3.0	0 / 3.1	* / 0	* / 0
8814-Ru	0 / 1.8	0 / 1.8	* / 0	36 / 0.7

CPDD 0061 was administered via nasogastric tube at various time points (120-240 min) prior to testing. Doses of CPDD 0061 were tested once. *No completed trials. See Table 1 for other details.

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations)

In monkeys receiving diazepam daily and discriminating between flumazenil and vehicle, administration of CPDD 0061 (100, 178 and 320 mg/kg) at the beginning of 2-hr sessions did not substitute (i.e. produce ≥80% DR) for the flumazenil discriminative stimulus (Table 9). In monkey DA, a dose of 178 mg/kg of CPDD 0061 substituted for flumazenil. Doses of 100 and 178 mg/kg of CPDD 0061 did not alter response rate. A dose of 320 mg/kg of CPDD 0061 substantially decreased response rate in one monkey (ROL) and suppressed responding in two other monkeys (DA and JI).

Table 9 Discriminative stimulus effects of CPDD 0061 in diazepam (5.6 mg/kg/day) treated rhesus monkeys discriminating flumazenil: dose response

Subject	CPDD 0061 Dose (mg/kg) 100	CPDD 0061 Dose (mg/kg) 178	CPDD 0061 Dose (mg/kg) 320
DA	3 / 1.55	88 / 1.17	* / 0
ROL	5 / 1.69	5 / 1.20	* / 0.06
JI	0 / 1.87	0 / 1.61	* / 0

CPDD 0061 was administered at the beginning of a 2-hr session; data are the average of four cycles from the second hr. *Discrimination data are not presented when response rate was <20% of control response rate. nt=not tested. See Table 3 for other details.

In monkeys discriminating between midazolam and saline, administration of CPDD 0061 (100, 178, 320 and 560 mg/kg) at the beginning of 2-hr sessions did not substitute (i.e. produce ≥80% DR) for the midazolam discriminative stimulus in any monkey (Table 10). A dose of 100 mg/kg of CPDD 0061 did not alter response rate. A dose of 178 mg/kg of CPDD 0061 suppressed responding in one monkey (RO), 320 mg/kg decreased response rate in another monkey (SA), and 560 mg/kg suppressed responding in the third monkey (LI).

Table 10 Discriminative stimulus effects of CPDD 0061 in rhesus monkeys discriminating midazolam: dose response

Subject	CPDD 0061 Dose (mg/kg)			
	100	178	320	560
RO	1 / 1.98	* / 0	nt	nt
LI	0 / 1.45	0 / 1.34	0 / 1.35	* / 0
SA	0 / 1.95	0 / 1.95	0 / 0.96	nt

CPDD 0061 was administered at the beginning of a 2-hr session; data are the average of four cycles from the second hr. *Discrimination data are not presented when response rate was <20% of control response rate. nt=not tested. See Table 5 for other details.

CPDD 0062

Melatonin

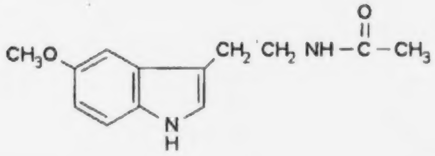
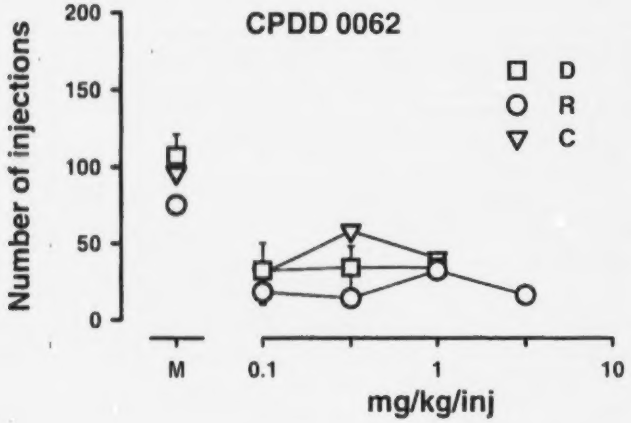


Figure 3 Self-administration of CPDD 0062 in monkeys experienced with methohexital



Reinforcing Effects in Rhesus Monkeys

Figure 3 shows results of self-administration studies with CPDD 0062 in three monkeys experienced with self-administration of methohexital. Each symbol designates the number of injections taken by the individual monkeys. The symbols over M represent the number of injections of sodium methohexital averaged over two sessions that occurred prior to evaluation of the first, smallest dose of CPDD 0061. Data for sessions in which saline was delivered contingent on responding are not shown and were typically 10-15 injections per session.

In each of the three monkeys, CPDD 0062 maintained low levels of responding across all tested doses; no reinforcing effect was shown by this drug at these doses.

Discriminative Stimulus Effects in Rhesus Monkeys (pentobarbital discrimination)

When administered 60 minutes before the session, CPDD 0062 engendered no drug-appropriate responding in pentobarbital-trained monkeys (Table 11) up to a dose of 30 mg/kg and there was no systematic effect on response rate. When pre-treatment time was changed to 30 or 120 minutes for the dose of 30 mg/kg, no drug appropriate

Table 11 Discriminative stimulus effects of i.g. administration of CPDD 0062 in monkeys discriminating pentobarbital: dose response

Subject	Pentobarbital	Saline	CPDD 0062 Dose (mg/kg) 1	3	10	30
Ef3-E	100 / 2.2	3 / 2.5	3 / 2.4	0 / 2.6	1.5 / 2.9	0 / 2.4
AQ63-G	100 / 2.2	0 / 3.0	nt	0 / 2.5	0 / 3.4	0 / 2.7
17015-Ro	96 / 2.1	5 / 2.4	nt	nt	0 / 2.8	0 / 2.8
8814-Ru	100 / 1.3	0 / 2.0	0 / 2.0	nt	0 / 1.9	0 / 1.9

CPDD 0062 was administered via nasogastric tube 60 minutes prior to testing. Doses of CPDD 0062 were generally tested once. nt=not tested. See Table 1 for other details.

Table 12 Discriminative stimulus effects of i.g. administration of CPDD 0061 in monkeys discriminating pentobarbital: time course

Subject	CPDD 0062 (30 mg/kg) Time (min) 30	120
Ef3-E	0 / 2.6	0 / 2.5
AQ63-G	0 / 2.8	0 / 2.9
17015-Ro	0 / 3.0	0 / 3.0
8814-Ru	0 / 1.8	0 / 1.7

CPDD 0062 (30 mg/kg) was administered via nasogastric tube at various time points (30 or 120 min) prior to testing. Doses of CPDD 0062 were tested once. See Table 1 for other details.

Responding was seen, and there was no systematic effect on response rate (Table 12). Thus, CPDD 0062 did not have pentobarbital-like discriminative stimulus effects in rhesus monkeys when administered i.g. in doses up to 30 mg/kg.

Discriminative Stimulus Effects in Rhesus Monkeys (flumazenil and midazolam discriminations)

In monkeys receiving diazepam daily and discriminating between flumazenil and vehicle, administration of CPDD 0062 (32 and 100 mg/kg) at the beginning of 2-hr sessions did not substitute (i.e. produce ≥80% DR) for the flumazenil discriminative stimulus in two diazepam treated monkeys (Table 13). CPDD 0062 (32 and 100 mg/kg) did not alter response rate.

Table 13 Discriminative stimulus effects of CPDD 0062 in diazepam (5.6 mg/kg/day) treated rhesus monkeys discriminating flumazenil: dose response

Subject	CPDD 0062 Dose (mg/kg) 32	 100
DA	2/ 1.75	0 / 1.21
ROL	1 / 1.52	1 / 1.13

CPDD 0062 was administered at the beginning of a 2-hr session; data are the average of four cycles from the second hr. See Table 3 for other details.

In monkeys discriminating between midazolam and saline, administration of CPDD 0062 (32 and 100 mg/kg) at the beginning of 2-hr sessions did not substitute (i.e. produce ≥80% DR) for the midazolam discriminative stimulus in two monkeys; however, a dose of 100 mg/kg of CPDD 0062 occasioned 75% midazolam-lever responding in one monkey (RO; Table 14). CPDD 0062 (32 and 100 mg/kg) did not alter response rate.

Table 14 Discriminative stimulus effects of CPDD 0062 in rhesus monkeys discriminating midazolam: dose response

Subject	CPDD 0062 Dose (mg/kg) 32	 100
RO	0 / 2.06	75 / 2.46
LI	0 / 1.94	0 / 1.74

CPDD 0062 was administered at the beginning of a 2-hr session; data are the average of four cycles from the second hr. See Table 5 for other details.

CONCLUSIONS

CPDD 0060

In self-administration studies, CPDD 0060 (1,4-butanediol; 1,4-BDL) failed to maintain responding at rates above those maintained by saline in three of four monkeys. Solubility limits precluded self-administration studies on doses of CPDD 0060 larger than 3.2 mg/kg/injection. CPDD 0060 also failed to substitute for a flumazenil discriminative stimulus in diazepam-treated monkeys or for a pentobarbital or midazolam discriminative stimulus in untreated monkeys, up to doses that decreased response rates. While it is possible that other doses of CPDD 0060 might have reinforcing effects or discriminative stimulus effects under other conditions, in the current studies CPDD 0060 was not a positive reinforcer in most monkeys and did not exert pentobarbital-like, midazolam-like or benzodiazepine antagonist-like discriminative stimulus effects in rhesus monkeys.

CPDD 0061

In self-administration studies, CPDD 0061 (gamma-butyrolactone; GBL) failed to maintain responding at rates above those maintained by saline in two of three monkeys. Solubility limits precluded self-administration studies on doses of CPDD 0061 larger than 3.2 mg/kg/injection. CPDD 0061 did not substitute for a pentobarbital or midazolam discriminative stimulus in untreated monkeys, up to doses that decreased response rates. While it is possible that other doses of CPDD 0061 might have reinforcing effects or discriminative stimulus effects under other conditions, in the current studies CPDD 0061 was not a positive reinforcer and did not exert pentobarbital-like or midazolam-like discriminative stimulus effects in rhesus monkeys. CPDD 0061 substituted for a flumazenil discriminative stimulus in one of three diazepam-treated monkeys suggesting that this compound might have benzodiazepine antagonist-like discriminative stimulus effects.

CPDD 0062

In self-administration studies, CPDD 0062 (melatonin) failed to maintain responding at rates above those maintained by saline. Solubility limits precluded self-administration studies on doses of CPDD 0062 larger than 3.2 mg/kg/injection. CPDD 0062 did not substitute for a flumazenil discriminative stimulus in diazepam treated monkeys or for a pentobarbital or midazolam discriminative stimulus in untreated monkeys. While it is possible that other doses of CPDD 0062 might have reinforcing effects or discriminative stimulus effects under other conditions, in the current studies CPDD 0062 was not a positive reinforcer and did not exert pentobarbital-like, midazolam-like or benzodiazepine antagonist-like discriminative stimulus effects in rhesus monkeys.

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WORKSHOP

NIDA MEDICATIONS DEVELOPMENT: NEW DIRECTIONS AND RESOURCES FOR MEDICINAL CHEMISTS TARGETING BIOGENIC AMINE TRANSPORTERS

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This workshop was aimed at medicinal chemists and their pharmacologist collaborators who are focusing on biogenic amine transporters as targets for medication discovery. Its goal was to facilitate the discovery of novel transporter-directed medications for treating cocaine and other drug dependence disorders. A new method for visualizing transporter selectivity, with regard to activity at the 3 different transporters (DAT, NET and SERT), was presented. This method was then used to visualize the transporter selectivity of clinical compounds, as well as hundreds of novel transporter compounds submitted to NIDA's Cocaine Treatment Discovery Program over the past decade, and "gap areas" in transporter selectivity were identified. These gap areas represent transporter selectivity profiles for which there are no available compounds and, therefore, they may serve to focus new medication discovery efforts. The theoretical pros and cons of including DAT, NET, and/or SERT inhibition activity in potential medications were presented and the theoretical rationale (beyond "novelty") for pursuing the discovery of compounds with transporter selectivity profiles corresponding to gap areas was discussed. Finally, NIDA contract resources available to chemists to support compound testing were summarized. Due to page limitations, this summary will primarily focus on a description of the new method for visualizing transporter selectivity and on the identification of gap areas. Readers are urged to contact NIDA with any questions regarding contract resources available to support medication discovery efforts.

Table 1 shows the potencies of clinical biogenic amine uptake inhibitors in assays measuring inhibition of radioligand binding to biogenic amine transporters as well as potencies for inhibiting the uptake of labeled neurotransmitters. These data will be used to demonstrate the method for visualizing transporter selectivity.

Transporter selectivity graphs can be constructed using data from either binding or uptake studies. Figures 1 through 4 demonstrate the approach that is taken for data from binding studies. In these Figures, the ratio of DAT K_i/SERT K_i is plotted on the x-axis and the ratio of DAT K_i/NET K_i is plotted on the y-axis.

Relationships between affinities at the DAT and the SERT are defined by lines drawn perpendicular to the x-axis (Figure 1). Compounds showing greater than 100-fold preference for the DAT (vs. the SERT) will fall to the left of line A. Compounds showing greater than 100-fold preference for the SERT (vs. the DAT) will fall to the right of line D. Compounds showing affinities at the DAT and the SERT that are within 3-fold of each other (compounds showing similar affinities at the DAT and the SERT) will fall between lines B and C.

In a similar fashion, relationships between affinities at the DAT and the NET are defined by lines drawn perpendicular to the y-axis (Figure 2). Compounds showing greater than 100-fold preference for the NET (vs. the DAT) will fall above line E. Compounds showing greater than 100-fold preference for the DAT (vs. the NET) will fall below line H. Compounds showing affinities at the DAT and the NET that are within 3-fold of each other will fall between lines F and G.

Lines used to define relationships between affinities at the NET and the SERT (Figure 3) are not intuitively obvious from the x- and y-axes but, specific points may be plotted and then connected to define desired boundaries. For example, the line that represents 100-fold preference for the NET (vs. the SERT) may be found by connecting the point for a theoretical drug with NET $K_i = 1$ nM, SERT $K_i = 100$ nM, and DAT $K_i = 1$ nM ($x, y = 0.01, 1$) and the point for a theoretical drug with NET $K_i = 1$ nM, SERT $K_i = 100$ nM, and DAT $K_i = 100$ nM ($x, y = 1, 100$); this results in line I. Compounds showing greater than 100-fold preference for the NET (vs. the SERT) will fall above line I. Lines J, K, and L may be derived in a similar fashion. Compounds showing greater than 100-fold preference for the SERT (vs. the NET) will fall below line L. Compounds showing affinities at the NET and the SERT that are within 3-fold of each other will fall between lines J and K.

The seven shaded regions in Figure 4 are constructed from lines A through L in Figures 1 through 3 and they represent specific transporter selectivity profiles. When points for compounds are plotted, Region D encompasses compounds that are highly selective for binding to the DAT. Region N encompasses compounds that are highly selective for binding to the NET. Region S encompasses compounds that are highly selective for binding to the SERT. Region DN encompasses compounds that bind with similar affinities to the DAT and the NET (K_i values are within 3-fold) and that are highly selective for binding to these two transporters when compared to the SERT. Region DS encompasses compounds that bind with similar affinities to the DAT and the SERT and that are highly selective for binding to these two transporters when compared to the NET. Region NS encompasses compounds that bind with similar affinities to the NET and the SERT and that are highly selective for binding to these two transporters when compared to the DAT. Finally, region DNS encompasses compounds that are truly non-selective, binding with similar affinities at all three transporters. A similar graph may be constructed for plotting data from biogenic amine uptake inhibition studies by using uptake IC_{50} ratios rather than binding K_i ratios.

Table 1. Potencies of clinical biogenic amine uptake inhibitors in assays measuring inhibition of radioligand binding to the DAT, the NET and the SERT and in assays measuring the inhibition of [3H]dopamine uptake by the DAT, [3H]norepinephrine uptake by the NET, and [3H]serotonin uptake by the SERT. Unless otherwise noted, values are from Eshleman et al. (1999).

No.	Compound Name	Binding Inhibition K_i (nM)			Uptake Inhibition IC_{50} (nM)		
		DAT	NET	SERT	[^{3}H]DA	[^{3}H]NE	[^{3}H]5HT
1	Amitriptyline	3,250[a]	35[a]	4.3[a]	2,300[b]	24[b]	66[b]
2	Amoxapine	4,310[a]	16[a]	58[a]	1,900[b]	4.4[b]	470[b]
3	Benztropine	293	4,000	15,800	42	292	47,000
4	Bupropion	2,630	20,700	34,600	2,900	1,450	47,000
5	BW 306	-	-	-	23,000[c]	7,000[c]	10,5000[c]
6	BW 494	-	-	-	47,000[c]	16,000[c]	67,000[c]
7	Citalopram	28,100[a]	4,070[a]	1.16[a]	28,000[b]	4,000[b]	1.3[b]
8	Clomipramine	2,190[a]	38[a]	0.28[a]	1,800[b]	28[b]	5.4[b]
9	Cocaine	370	1,600	403	278	910	410
10	Desipramine	14,600	13.9	55.4	82,000	4.2	64
11	Doxepin	12,100[a]	29.5[a]	68[a]	5,700[b]	19[b]	280[b]
12	Fluoxetine	6,670	1,560	1.14	19,500	1,020	7.3
13	GBR-12909	14.2	540	385	22.4	235	6,800
14	Imipramine	25,500	215	3.32	25,600	70	8
15	Maprotiline	1,000[a]	11.1[a]	5,800[a]	2,900[b]	7.4[b]	3,300[b]
16	Methylphenidate	184	1,770	40,400	193	37.7	55,000
17	Nefazadone	360[a]	360[a]	200[a]	2,380[d]	570[d]	137[d]
18	Nortriptyline	4,030	7.5	33	14,500	3.5	168
19	Paroxetine	490[a]	40[a]	0.13[a]	1,700[d]	33[d]	0.73[d]
20	Protriptyline	2,100[a]	1.41[a]	19.6[a]	1,850[b]	0.97[b]	280[b]
21	Sertraline	25[a]	420[a]	0.29[a]	260[d]	220[d]	3.4[d]
22	Trazodone	7,400[a]	8,500[a]	160[a]	14,000[b]	5,000[b]	190[b]
23	Trimipramine	3,780[a]	2,450[a]	149[a]	3,400[b]	510[b]	2,500[b]
24	Venlafaxine	9,300[a]	1,060[a]	8.9[a]	5,300[d]	210[d]	39[d]

[a] Tatsumi et al. (1997)
[b] Richelson and Pfenning (1984)
[c] Ascher et al. (1995)
[d] Bolden-Watson and Richelson (1993)

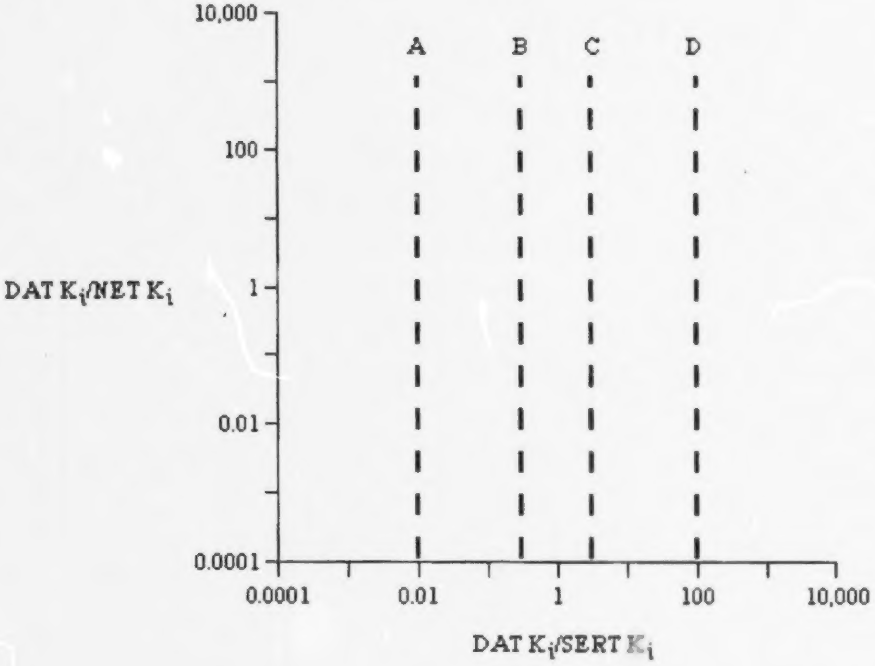

Figure 1. Lines defining relationships between affinities at the DAT and the SERT. See text for related discussion.

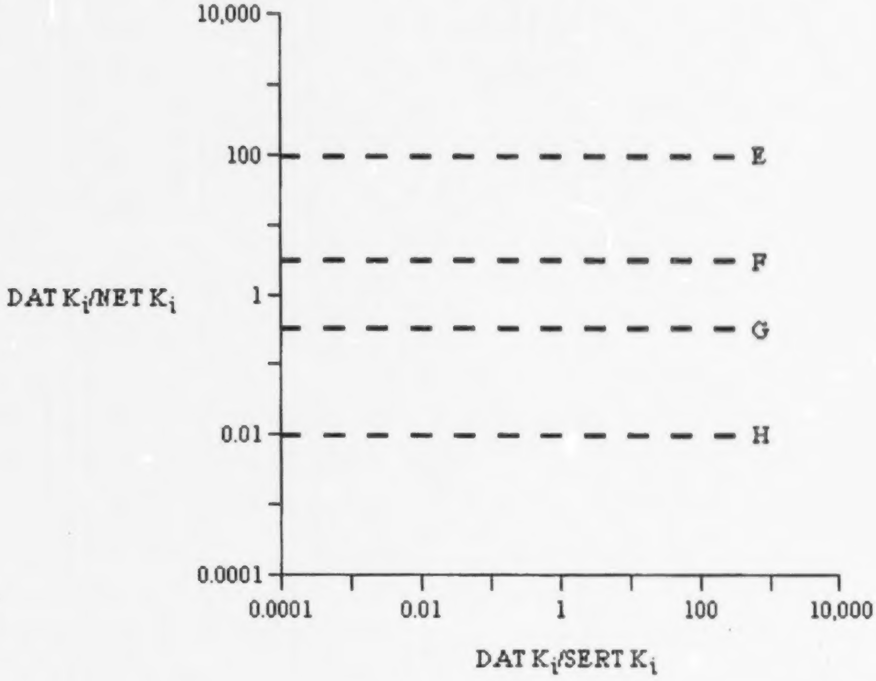

Figure 2. Lines defining relationships between affinities at the DAT and affinities at the NET. See text for related discussion.

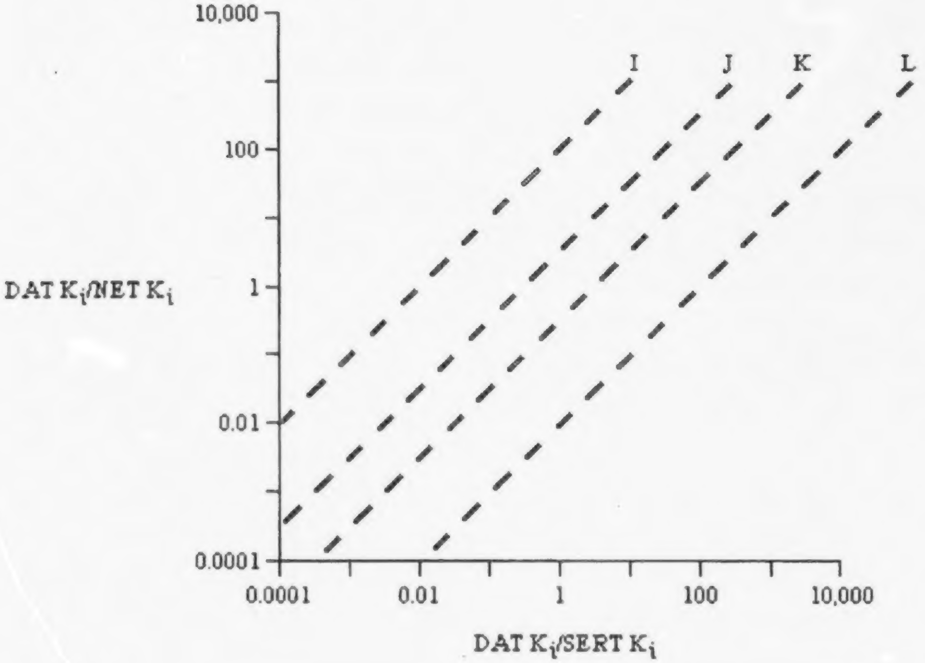

Figure 3. Lines defining relationships between affinities at the NET and affinities at the SERT. See text for related discussion.

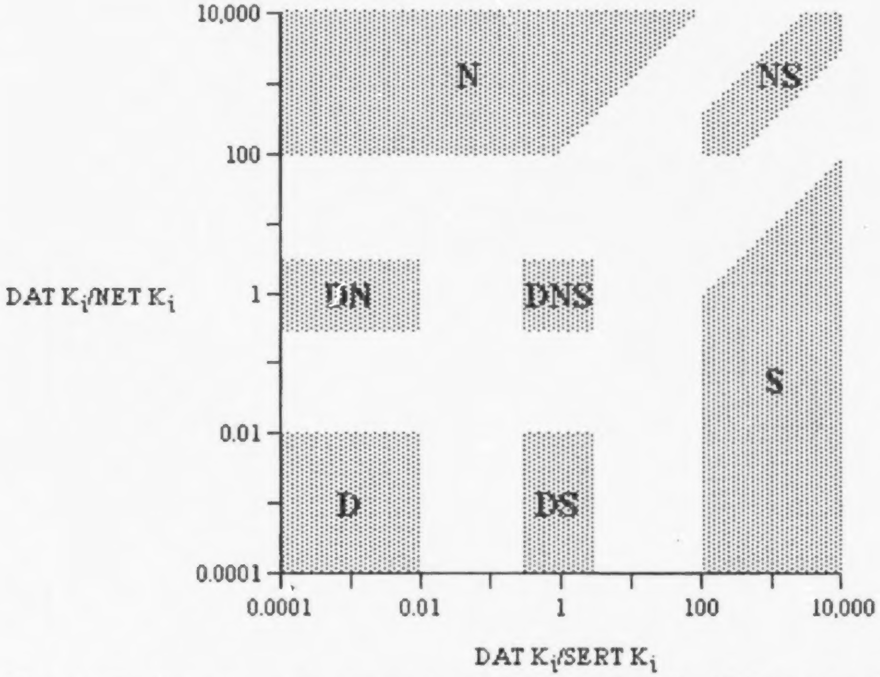

Figure 4. Regions representing transporter selectivity profiles. N = NET-selective, D = DAT-selective, S = SERT-selective, NS = comparable affinity at the NET & the SERT with relatively no affinity at the DAT, etc.

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Figure 5 shows the selectivity of the compounds listed in Table 1 for inhibiting radioligand binding to biogenic amine transporters and Figure 6 shows the selectivity of these same compounds for inhibiting biogenic amine uptake. As described above, in developing this method for visualizing transporter selectivity, a compound was defined as "selective" for one transporter vs. another if the separation between K_i values for inhibition of radioligand binding is greater than 100-fold (or if the separation between IC_{50} values for inhibition of [^{3}H] amine uptake is greater than 100-fold). Viewing the points for compounds regarded as selective serotonin reuptake inhibitors (SSRIs), this graphical definition of selectivity (e.g., represented by the borders of the S region) appears appropriate; points for citalopram (7), fluoxetine (12), paroxetine (19) and sertraline (21) all fall within or on the borders of region S in both Figures 5 and 6.

In both Figures 5 and 6, trazodone (22) appears to be as selective an inhibitor of 5HT uptake as the four established SSRIs. Trazodone is not regarded as an SSRI because of its prominent activity as a 5HT-2 receptor antagonist. This raises an important point that must be kept in mind when viewing selectivity plots such as those shown in Figures 5 and 6; activities at sites other than biogenic amine transporters are not reflected in the graphs. Nefazadone (17) provides another example. Despite the fact that nefazadone falls into the DNS region in Figure 5, this drug's prominent 5HT-2 and D-2 antagonist activities make it a poor research tool for evaluating the effects of non-selective biogenic amine uptake inhibitors in animal models of cocaine addiction or in clinical trials for the treatment of cocaine dependence. While nefazadone has merited evaluation in such studies, its effectiveness (or lack of effectiveness) cannot be extrapolated to the general category of non-selective biogenic amine uptake inhibitors. For medicinal chemists synthesizing novel compounds in an effort to achieve a specific transporter selectivity [e.g., for those working to discover selective dopamine reuptake inhibitors (SDRIs)], transporter selectivity plots similar to Figures 5 and 6 may provide a convenient means to compare large series of compounds; however, once the desired selectivity is observed in such plots, broad receptor profiling must be conducted to establish a compound's full selectivity profile. Given the propensity of many biogenic amine uptake inhibitors to bind to histaminergic, adrenergic and muscarinic cholinergic receptors (with benztropine providing and extreme example of the latter), the discovery of selective uptake inhibitors is a challenging endeavor.

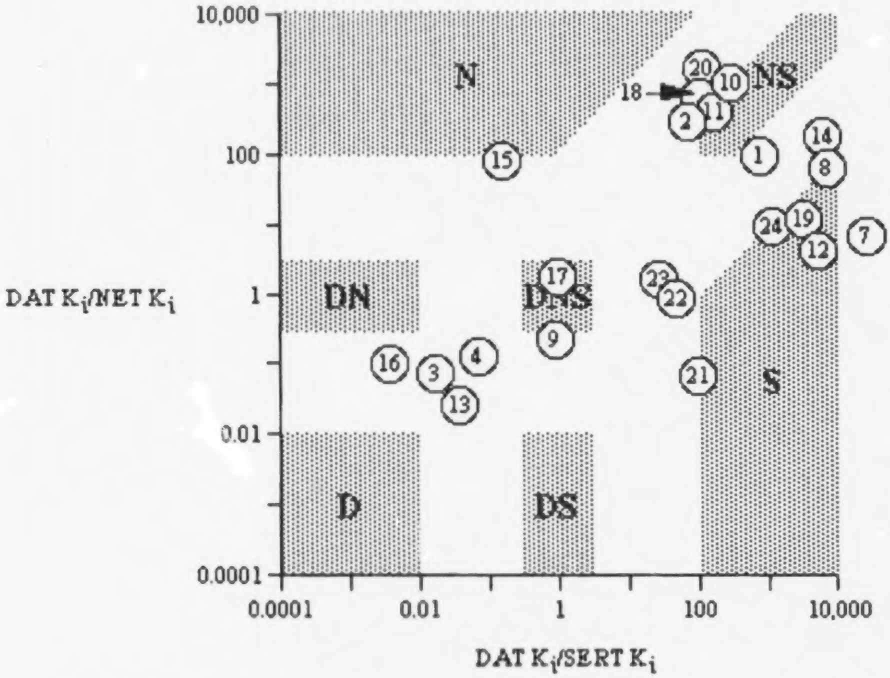

Figure 5. Selectivity plot of compounds in Table 1 using data for inhibition of radioligand binding to the DAT, the NET and the SERT.

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It is apparent from Figures 5 and 6 that no clinically available biogenic amine uptake inhibitors fall into regions D or DS of the selectivity plots. GBR-12909 (13) has often been referred to as "DAT-selective"; however, if we use a greater than 100-fold separation in affinity to define "selectivity" (see above re SSRIs), then GBR-12909 cannot be regarded as an SDRI. In addition, GBR-12909 is active at a number of receptors and ion channels. For example, broad receptor profiling of GBR-12909 revealed K_i values of 69 nM at H-1 receptors, 101 nM at D-4 receptors, and 140 nM at L-type Ca^{++} channels (NIDA contract N01DA-8-8089 with NovaScreen). Thus, the selectivity profiles represented by regions D and DS represent potentially important gap areas, for which no biogenic amine uptake inhibitors are clinically available. By working to eliminate activity at the NET while maintaining activity at the DAT, chemists may discover uptake inhibitors compounds with novel selectivity profiles that merit consideration for development as treatments for cocaine dependence.

There are multiple lines of evidence suggesting that inhibition of the NET may be undesirable in a cocaine dependence treatment medication. One important issue involves the potential for adverse cardiovascular interactions of NET inhibitors with cocaine. While cocaine itself inhibits the reuptake of NE as well as 5HT and DA, the known effects of NET inhibition (and the resulting stimulation of adrenergic receptors) on the cardiovascular system may interact with cocaine's actions to increase blood pressure and heart rate. Although the complexity and regional specificity of the adrenergic system does not lend itself to simplistic interpretation of the effects of increased noradrenergic tone, NET inhibition has been linked to the syndrome of orthostatic intolerance, which includes changes in the regulation of vascular tone and increases in basal blood pressure (Schroeder et al. 2002). Further, the pathogenesis of hypertension has been linked to increased levels of NE and prolongation of NE clearance rate in heart, kidneys, and vasculature as a result of NET dysfunction (Esler et al. 2001). Finally, high doses of tricyclic antidepressants, which inhibit both NET and SERT, have been reported to increase heart rate and prolong QT and QRS complexes in cardiac rhythm (Rawling and Fozzard 1979, Glassman and Bigger 1981).

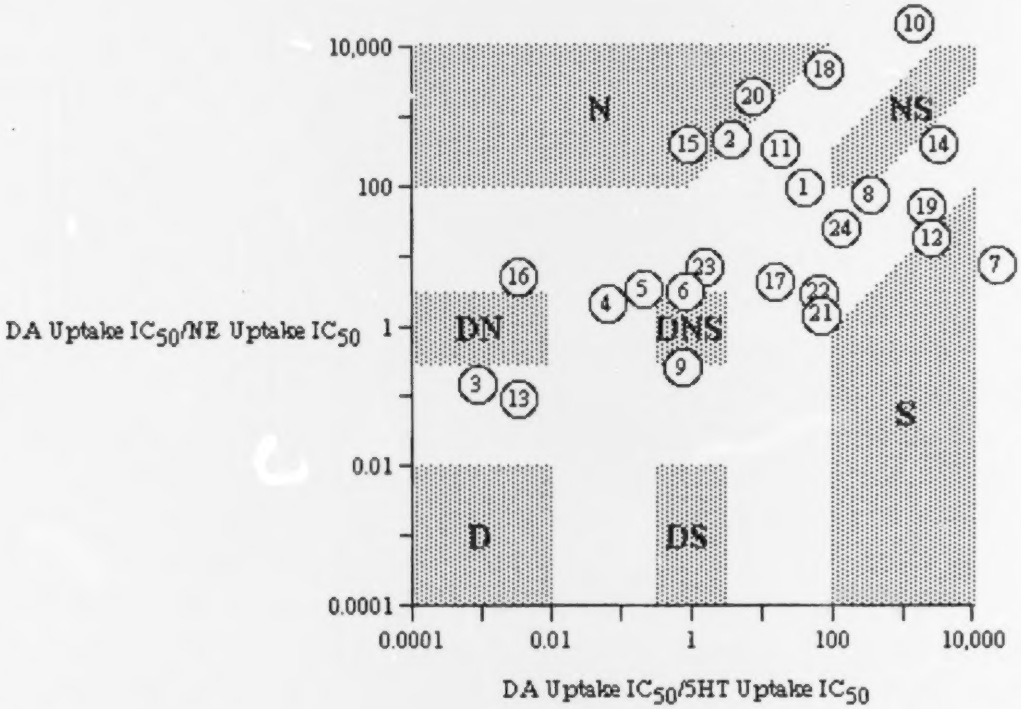

Figure 6. Selectivity plot of compounds in Table 1 using data for inhibition of [^{3}H]dopamine uptake by the DAT, inhibition of [^{3}H]norepinephrine uptake by the NET, and inhibition of [^{3}H]serotonin uptake by the SERT.

The fact that noradrenergic neurotransmission is part of the cascade of events involved in stress responses provides a second argument for avoiding NET inhibition in a cocaine dependence treatment medication. Stress is widely believed to be a trigger for craving and relapse to cocaine use in humans (Sinha et al. 1999, Wallace 1989), and has been reliably shown to reinstate previously extinguished self-administration of cocaine in rats (Erb et al. 1996; Ahmed and Koob 1997; Shaham et al. 2000). The association of inhibition of NE reuptake with exacerbation of the stress response has been reported anecdotally following administration of selective NE uptake inhibitors (Chouinard et al. 1984), and may be a logical consequence of inhibition of NE uptake, given that certain adrenergic antagonists can block stress-induced reinstatement in rats (Shaham et al. 2000). Therefore, in seems possible that inhibition of the NET by a medication prescribed in a effort to treat cocaine dependence might potentiate the noradrenergic component of the stress response, increasing the risk of relapse to cocaine use while in treatment.

Given the theoretical advantages of avoiding activity at the NET in a medication for treating cocaine dependence, NIDA's Cocaine Treatment Discovery Program is working to identify novel compounds that are either DAT-selective (fitting into region D of the selectivity plots) or DAT- and SERT-selective (fitting into region DS of the selectivity plots). Such compounds would merit evaluation in animal models of cocaine addiction and would possibly merit preclinical safety testing in support of future clinical trials. Selectivity plots of transporter binding data corresponding to more than 800 biogenic amine uptake inhibitors submitted to the Program over the past decade (data not shown) revealed eight compounds falling into region D and no compounds falling into region DS. Selectivity plots of data from uptake inhibition studies for the same set of compounds (data not shown) revealed no compounds falling into regions D or DS. Thus, eight compounds met DAT-selective criteria when only K_i values for inhibition of radioligand binding to the transporters were considered but, none of these compounds met DAT-selective criteria when IC_{50} values for inhibition of biogenic amine uptake were considered. In almost all cases, these compounds were much more potent at inhibiting [^{3}H]NE uptake than would be expected from their corresponding NET radioligand binding assay results. Similar differences are seen for benztropine, bupropion and methylphenidate in Table 1 (IC_{50} values for inhibiting [^{3}H]NE uptake are much lower than K_i values for inhibiting radioligand binding to the NET). An extreme example of how such a difference between binding and uptake assay results can affect the apparent selectivity of a compound is provided by Kuhar et al. (1999); for the phenyltropane RTI-113, binding IC_{50} values were reported to be 2.0, 2,950 and 2,330 nM at the DAT, NET and SERT, respectively (corresponding to a greater than 1000-fold selectivity for the DAT) while uptake IC_{50} values were reported to be 3.0, 31, and 229 nM for [^{3}H]DA, [^{3}H]NE and [^{3}H]5HT, respectively (corresponding to only about a 10-fold preference for inhibiting the DAT vs. the NET). With such differences, which data (uptake or binding) should be used to judge transporter selectivity? The conservative answer would appear to be "both"; if a chemist wishes to work toward discovery of a compound exhibiting a specific transporter selectivity profile (e.g., "D" or "DS"), then supporting data from both radioligand binding and uptake studies will leave little room for debate.

To date, no compounds appear to meet the "D" or "DS" classification when both binding and uptake studies are considered. Work continues in this effort and chemists are encouraged to submit novel compounds for free, confidential testing in NIDA's Cocaine Treatment Discovery Program. Although medications that inhibit the NET have been used clinically for many years and have a number of therapeutic effects, it may be useful to eliminate NET inhibition in biogenic amine uptake inhibitors for development as treatments for cocaine dependence. Research suggests that they have the potential to exacerbate the cardiovascular effects of cocaine and they may exacerbate the effects of stress on relapse.

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